# Can We Predict Remission in Children with Juvenile Idiopathic Arthritis?

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

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**2018**

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# List of Abbreviations

| Acronym | Definition |
| --- | --- |
| ACR | American College of Rheumatology |
| ACR Pedi | American College of Rheumatology Paediatric |
| ACPA | Anti-citrullinated protein antibody |
| AFLAR | African League Against Rheumatism |
| AJC | Active joint count |
| ANA | Anti-nuclear antibodies |
| Anti-CCP | Anti-cyclic citrullinated peptide |
| APLAR | Asia Pacific League of Associations for Rheumatology |
| BSPAR | British Society for Paediatric and Adolescent Rheumatology |
| C-section | Caesarean-section |
| CAPS | Childhood Arthritis Prospective Study |
| CHAQ | Childhood Health Assessment Questionnaire |
| CHQ | Child Health Questionnaire |
| CI | Confidence interval |
| CID | Clinically inactive disease |
| cJADAS | Clinical Juvenile Arthritis Disease Activity Score |
| COMET | Core Outcome Measures in Effectiveness Trials |
| COSMIN | Consensus-based Standards for the Selection for health Measurement Instruments |
| COV | Core outcome variable |
| CPRD | Clinical practice research datalink |
| CR | Clinical remission (off medication) |
| CRM | Clinical remission on medication |
| CRP | C-reactive protein |
| csDMARD | Conventional synthetic disease modifying anti-rheumatic drug |
| CYP | Children and young people/child or young person |
| DMARD | Disease modifying anti-rheumatic drug |
| EMA | European Medicines Agency |
| ERA | Enthesitis-related arthritis |
| ESR | Erythrocyte sedimentation rate |
| EULAR | European League Against Rheumatism |
| GP | General practitioner |
| GWAS | Genome-wide association study |
| HAQ | Health Assessment Questionnaire |
| HES | Hospital Episode Statistics |
| HLA | Human leukocyte antigen |
| HRQoL | Health-related quality of life |
| IA | Intra-articular |

| Acronym | Definition |
| --- | --- |
| IBD | Inflammatory bowel disease |
| IgG | Immunoglobulin G |
| IL | Interleukin |
| IMD | Index of multiple deprivation |
| IQR | Interquartile range |
| ILAR | International League of Associations for Rheumatology |
| JADAS | Juvenile Arthritis Disease Activity Score |
| JADI-A | Juvenile Arthritis Damage Index – Articular |
| JAMAR | Juvenile Arthritis Multidimensional Assessment Report |
| JAS | Juvenile ankylosing spondylitis |
| JCA | Juvenile chronic arthritis |
| JIA | Juvenile idiopathic arthritis |
| JRA | Juvenile rheumatoid arthritis |
| LJC | Limited joint count |
| LOCF | Last observation carried forward |
| NGT | Nominal group technique |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NSAID | Non-steroidal anti-inflammatory drug |
| MAR | Missing at random |
| MCAR | Missing completely at random |
| MCID | Minimally clinically important difference |
| MDA | Minimal disease activity |
| MHC | Major histocompatibility complex |
| MNAR | Missing not at random |
| MTX | Methotrexate |
| OMERACT | Outcome Measures in Rheumatology |
| OR | Odds ratio |
| PANLAR | Pan American League of Associations for Rheumatology |
| PICO | Patient Intervention Comparison Outcome |
| PGA | Physician's global assessment |
| PGE | Parental global evaluation |
| PsA | Psoriatic arthritis |
| QA | Quality assessment |
| QALY | Quality-adjusted life year |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| SD | Standard deviation |
| SNP | Single nucleotide polymorphism |
| T2T | Treat to target |
| TNF | Tumour necrosis factor |
| UK | United Kingdom |
| VAS | Visual analogue scale |

# Abstract

**Background:** Long-term consequences of active disease in juvenile idiopathic arthritis (JIA) include persistent pain, disability and potential joint replacement surgery. The aims of treatment are therefore clinically inactive disease (CID) and, ideally, sustained disease remission. This thesis set out to understand CID and remission in JIA: how they are defined, how commonly they are achieved, long-term outcomes following their achievement and whether they are associated with factors early in disease.

**Methods:** The setting for this thesis was the UK Childhood Arthritis Prospective Study (CAPS), the largest multicentre, prospective inception cohort of JIA globally. Children and young people (CYP) were selected for each paper based on their dates of recruitment and categories of disease. At one year following initial presentation to paediatric rheumatology, CYP were classified as to whether they had fulfilled published criteria for CID. Initial analyses explored whether different definitions for CID identified the same groups of CYP. Outcomes to five years were then compared between those achieving all, some or none of the criteria for CID using multivariable, multilevel logistic (absence of limited joints), linear (quality of life) and zero-inflated negative binomial (functional ability) regression models. Finally, risk factors for remission (CID maintained over two annual follow-ups) were explored using multivariable logistic regression models. Throughout, multiple imputation under various assumptions was implemented for missing data.

**Results:** The majority of CYP in CAPS were female (65%) and had oligoarthritis (50%). Median age at initial presentation was eight years (IQR 4, 12). At one year, fewer than 50% of CYP had achieved CID according to published definitions. There was poor overlap (44%) between groups of CYP identified by two validated definitions, whose main difference was the inclusion or exclusion of patient-reported wellbeing. The odds of no limited joints in the long-term did not differ between CYP fulfilling either definition of CID. However, CYP who achieved CID on scores which included wellbeing had superior long-term function (OR for no disability: 2.5, 95% CI 1.8, 3.5) and quality of life (β: 3.9, 95% CI 1.6, 6.2) to those who either did not achieve CID or only achieved it using inflammatory criteria (i.e. had persistent symptoms despite the absence of inflammation). Finally, there were few factors at initial presentation which were associated with remission. However, greater improvements in both physician and patient-reported variables over the first year following initial presentation were associated with higher odds of remission in the first three years.

**Conclusions:** The disease burden in JIA remains high with over 50% of CYP not achieving CID within the first year of disease. Current definitions of CID available for use in clinical practice as potential treatment targets do not classify the same groups of CYP and are associated with different long-term outcomes. Further study is required to define the best outcome measures for CYP with JIA.

## Declaration

No portion of the work in this thesis has been submitted in support of an application for another degree or qualification at this or any other university of institute of learning.

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# Acknowledgements

I would like to thank a multitude of lovely people for supporting me through this process. Firstly I'd like to thank my amazing supervisors, Professor Kimme Hyrich, Dr Suzan Verstappen and Professor Wendy Thomson. This work is a testament to your endless knowledge and patience. Thank you for helping me see the woods rather than getting lost in the trees. Beyond this, I'd like to thank Professor Hyrich for indoctrinating me into the department's underground country music gang and for making me feel like family. I will never forget dancing with you, John and Elsa at my wedding. I'd also like to thank Dr Verstappen for introducing me to Nasi Goreng. I can only hope to also proudly display a qualification for sheepdog herding in my own office one day. Thanks to everyone in the Centre for Musculoskeletal Research for your encouragement and friendship, in particular the superstars in 2.707 and my fellow vet comrade Lianne Kearsley-Fleet.

I'd like to thank the academics who inspired me to become an epidemiologist in the first place. They include the wonderful Professor Nicola Williams, Professor David Brodbelt and Dr Dan O'Neill. You allowed me to pursue my dream job and for that I will always be in your debt.

None of this would have been possible without the children and young people with arthritis and their families. Thanks so much to you, the healthcare professionals, administrative and data management teams involved in CAPS.

Finally, I'd like to thank the most important people in my life. To my amazing mummy, there's nothing I could say to cover a lifetime of believing in me and encouraging me to be my best self. You're my role model. To my dad, after four years, I can confirm that I've found the answer! Look! I've written a whole book about it! I look forward to four more years with the next question and discussing the improvements in your table tennis backhand. To Rosie, I'm sorry for that one time I didn't eat my vegetables and then blamed you. I've felt guilty about that for 20 years. Thanks for putting up with a disloyal sister all this time and continuing to make the best baked goods north of the M25. To my almost-brothers, Philip and Robbie, and my surrogate mums Mary and Laura, I love you guys. You made my childhood and I won't ever, ever forget it. To my amazing friends Lucy, Elle and Emily and family Betty, Robert, Grandma Hettie, Kate, Claire, Nick, Vanessa, Jo, Matthew, Sue and John, you guys never cease to be proud of me no matter what rubbish comes out of my mouth. I hope Grandpa Basil would be proud too. A quick word for Galaxy, with whom I've chatted every morning. She might not have understood a word, being a horse, but helped me de-stress to no end. Finally, I'd like to thank the love of my life, my comrade in snuggles, silly dancing and now Football (MEDIA) Lecturer Extraordinaire. My wonderful Christopher, I'm sorry for making you read that dissertation on water. And I'm sorry for making you proofread this too. You make my life.

# Preface

In 2013, I graduated from the University of Liverpool with a BSc in Bioveterinary Science. It was here that I took my first Epidemiology module and gained a passion for the critical analysis of published research and the exploration of patterns within chronic disease data. During this degree, I worked as a Research Assistant within the University of Liverpool's Department of Epidemiology and Population Health under Professor Nicola Williams. I spent my time getting frozen hands in sample storage, spinning bacterial growth plates and analysing data on antimicrobial resistance in canines with dermatological disorders. After graduating, I worked as a VetCompass Research Assistant within the Royal Veterinary College's Centre for Veterinary Epidemiology, Economics and Public Health under Professor David Brodbelt and Dr Dan O'Neill. I was fortunate to have the opportunity to work with VetCompass data, which covers over 10 million companion animal primary-care electronic medical records in the UK. In 2014, I made a move to human animals and graduated from Imperial College London with an MSc in Epidemiology (Biostatistics). I was then fortunate to gain this PhD placement, allowing me to develop my analytical skills in complex epidemiological datasets and make an impact on the health of young people with arthritis.

## Role of Candidate in this PhD

I undertook the following roles within this PhD:

- Design and development of research questions
- Development of statistical analysis plans
- Data extraction, cleaning and preparation
- Statistical analysis
- Interpretation of results
- Presentation of results in poster and oral format at national and international conferences
- Write up of results into manuscripts for publication
- Liaising with patient and public engagement groups
- Formulation of results into public engagement publications and presentations
- Writing of this thesis

# Journal Format

This thesis is written in journal format. The results chapters are therefore presented as complete manuscripts, three of which have already been published at the time of submission. Each results chapter therefore constitutes a separate paper, answering a specific research question regarding the understanding of remission in juvenile idiopathic arthritis. Corresponding journals were contacted for each published paper and no additional permissions were required to reproduce the papers as result chapters in this thesis. Each paper is formatted in the same style as the rest of this thesis to assist flow:

**Section 6.1: Published in Seminars in Arthritis and Rheumatism**

Shoop-Worrall SJW, L Kearsley-Fleet, W Thomson, SMM Verstappen and KL Hyrich (2017). *How Common is Remission in Juvenile Idiopathic Arthritis: A Systematic Review*. Seminars in Arthritis and Rheumatism, 47(3): 331-337.

**Section 6.2: Published in Annals of the Rheumatic Diseases**

Shoop-Worrall SJW, SMM Verstappen, E Baildam, A Chieng, J Davidson, H Foster, Y Ioannou, F McErlane, LR Wedderburn, W Thomson and KL Hyrich (2017). *How Common is Clinically Inactive Disease in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis? The Importance of Definition.* Annals of the Rheumatic Diseases, 76(8): 1381-1388

**Section 6.3: Published in Arthritis and Rheumatology**

Shoop-Worrall SJW, SMM Verstappen, JE McDonagh, E Baildam, A Chieng, J Davidson, H Foster, Y Ioannou, F McErlane, LR Wedderburn, W Thomson and KL Hyrich (2018). *Long term Outcomes Following Achievement of Clinically Inactive Disease in Juvenile Idiopathic Arthritis: the Importance of Definition*. Arthritis and Rheumatology [epub ahead of print] doi: 10.1002/art.40519

**The final results chapter (Section 6.4) has been prepared for planned submission to Annals of the Rheumatic Diseases:**

Shoop-Worrall SJW, SMM Verstappen, JE McDonagh, E Baildam, A Chieng, J Davidson, H Foster, Y Ioannou, F McErlane, LR Wedderburn, W Thomson and KL Hyrich (2018). *Factors Associated with Remission in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis: The Importance of Definition*

# 1   INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease affecting children and young people (CYP). Whilst the aetiology is unknown, certain genetic and environmental factors have been reported to associate with the occurrence of this condition. The features of disease in JIA are primarily the inflammation of one or more synovial joints accompanied by pain and often limitation in function of the affected joint(s). There are seven defined disease categories with distinct manifestations of disease, including varying numbers of affected joints, serological abnormalities and specific extra-articular features such as psoriasis or enthesitis. If not controlled, chronic inflammation can lead to cartilage erosion and the eventual destruction of joints that may require replacement. In addition, long-term disease activity can result in functional limitations, chronic pain and impaired quality of life.

The severe consequences of unresolved JIA lend the ultimate goal of treatment to be complete remission. This would encompass the absence of inflammatory activity in addition to the resolution of the symptoms associated with active disease. However, there is no single gold standard test for remission. The heterogeneity in the features of JIA disease activity has resulted in the development of many definitions for remission, which each contain different components and have undergone variable levels of validation.

The ability to forecast disease course, including remission, would facilitate the early stratification of treatment in JIA. CYP less likely to achieve these states with current approaches to treatment could be targeted with more aggressive or alternative treatment strategies. This would maximise the early benefit of treatment and minimise the risk of adverse effects on cumulative, potentially unnecessary, therapies. The ability to measure and predict remission would also facilitate communication with patients and their guardians regarding expected outcomes.

It is currently unknown how many CYP with JIA achieve remission. Multiple definitions exist and there has not been a systematic review of the overall achievement of remission in JIA populations globally. Given the number of proposed definitions, each validated separately and rarely against each other, it is also unclear whether these definitions identify a common group of CYP, which would have implications for implementation in clinical practice. This group should be common in terms of both current disease states in addition to subsequent longer-term outcomes. Finally, few studies have assessed factors associated with remission early in the JIA disease course. Thus, there is a general lack of knowledge regarding how remission should be defined and the occurrence and predictors of remission

in general practice. Given these challenges, this thesis set out to explore the achievement, outcomes following and factors associated with remission states in CYP with JIA over the first five years of disease following diagnosis. The overall format of the thesis will flow according to Figure 1.

**Chapter 2**
- Epidemiology and Outcomes in JIA
  - This section focuses on the disease occurrence and processes in JIA, including potential treatment strategies. Outcomes measures are discussed, with a focus on measures of clinically inactive disease and remission.

**Chapter 3**
- Aims and Objectives

**Chapter 4**
- Methods
  - This section describes epidemiological principles considered when recruiting, selecting and analysing patient data in this thesis. Statistical analyses implemented to answer study aims and objectives are discussed.

**Chapter 5**
- The Childhood Arthritis Prospective Study
  - The demographic, clinical and patient-reported characteristics of participants selected for analyses in this thesis are described. In addition, missing data and differences in patients lost to follow-up under different mechanisms are detailed.

**Chapter 6**
- Results
  - Four manuscripts form the results chaper. These investigate the frequency of remission across clinical cohorts and within the Childhood Arthritis Prospective Study. In addition, long-term outcomes following, and factors associated with, remission are explored.

**Chapter 7**
- Discussion
  - This chapter discusses the key results of the thesis, including their clinical implications. Strengths and limitations of the analyses are examined, with reference to further research prompted by this work.

**Chapter 8**
- Final Conclusions

**Chapter 9**
- Appendices
  - Recruitment materials and questionnaires completed by both research nurses and participants/families are detailed.

**Figure 1.** Overall flow of chapters in this thesis

# Chapter 2

# Epidemiology and Outcomes in Juvenile Idiopathic Arthritis

*This chapter discusses the background to the classification and epidemiology of JIA, including risk factors for the development of this condition. Treatments are discussed with particular reference to anti-rheumatic therapies and proposed treatment pathways. Measures for assessing JIA disease activity, including single and composite outcome measures and definitions of remission are described. The occurrence of remission is the focus of a systematic review presented in Section 6.1; however reported predictors of remission in JIA are reviewed.*

## 2 EPIDEMIOLOGY AND OUTCOMES IN JUVNEILE IDIOPATHIC ARTHRITIS

### 2.1 What is Juvenile Idiopathic Arthritis?

Juvenile idiopathic arthritis (JIA) is a term used to describe a heterogeneous group of disorders with an onset prior to a child or young person's (CYP) 16th birthday. It is characterised by chronic inflammation (≥6 weeks) in one or more joints, with unknown aetiology [1]. The inflammatory mechanisms of the condition, which affects primarily synovial joints, have not been confirmed. However, affected joints are characterised by increased volumes of synovial fluid, containing inflammatory cells such as neutrophils, macrophages, dendritic cells and B- and T-type lymphocytes [2]. The invasion of synovial tissue by inflammatory cells and subsequent synovial cell hypertrophy and proliferation may cause its expansion [3], which along with the effect of destructive enzymes, can lead to cartilage and bone erosion with eventual destruction of the joint [4].

For some, JIA can be a relatively short-lived condition which responds easily to therapies, resulting in early remission [5]. For others, the disease can be more severe and persistent, resulting in chronic pain, joint damage and disability which will continue into adult life [6,7]. The goal of treatment for JIA is remission, since continued disease activity is associated with these poor long-term outcomes [4,6,7]. Currently, however, this state is not achieved by all CYP [5] and it is not yet possible to identify, with certainty, who will achieve remission.

#### 2.1.1 Classification of JIA

JIA is a clinical diagnosis based on a constellation of symptoms and signs. The heterogeneous nature of the disease has prompted the development of classification criteria to foremost aid research and communication, but which are also used to support clinical diagnoses. Over the years, three different criteria have been proposed (Table 1), with the current classification of JIA published under the auspices of the International League of Associations for Rheumatology (ILAR) in 2001 [1]. In all cases, the criteria have largely been driven by consensus opinion supported by clinical observations [1,8,9].

*Juvenile Rheumatoid Arthritis (JRA)*

The combination of signs and symptoms with which a CYP presents determines their JIA 'category' initially [1]. In certain forms of the disease, inflammation is localised to one or few joints and no extra-articular features are experienced (oligoarthritis). However, in around 25% of cases, greater than five joints are affected (polyarthritis) and in around 5% of cases, systemic manifestations such as fever, rash and splenomegaly may be experienced [4]. It was these differences in disease onset that, in 1972, initially led the

American College of Rheumatology (ACR) to sub-classify 'Juvenile Rheumatoid Arthritis' (JRA), as it was then called, into three categories: 'pauciarticular disease', where fewer than five joints were affected, 'polyarticular disease', where five or more joints were affected and 'systemic disease', where fever accompanied arthritis [8] (Table 1). In this original classification, psoriatic arthritis and enthesitis-related arthritis were not included.

### Juvenile Chronic Arthritis (JCA)

At a similar time to the ACR (1978), the European League Against Rheumatism (EULAR) also developed a classification system for 'Juvenile Chronic Arthritis' (JCA), as they named it, that mirrored the ACR criteria but differed slightly in regards to the 'systemic' criteria, and added three additional disease categories. The EULAR classification further separated CYPs that presented with enthesitis, sacroilitis and/or inflammatory bowel disease (IBD) in addition to their arthritis as 'enthesitis-related arthritis' and also defined a group with 'psoriatic arthritis' [9]. The final category added by EULAR was a category for CYP who did not fit into the other well-defined groups. They summarised this subgroup succinctly as 'undefined arthritis' [9] (Table 1).

### Juvenile Idiopathic Arthritis (JIA)

In later years, it became clear that an international, unified set of criteria was needed to classify patients with JRA and JCA alike, as different classifications for the same disease was complicating research and communication in this area [1,4]. In addition, subsequent experience with JRA and JCA patients had demonstrated additional disease manifestations and family history profiles commonly associated with the rarer EULAR categories. Furthermore, outcomes for patients in both the 'oligoarticular' and 'polyarticular' categories tended to follow one of two vastly different disease courses [1]. For these reasons, in 1995, ILAR defined classification criteria for JIA through a consensus meeting between 12 paediatric rheumatologists representing four international rheumatology bodies: EULAR, the Pan American League of Associations for Rheumatology (PANLAR), the Asia Pacific League of Associations for Rheumatology (APLAR) and the African League Against Rheumatism (AFLAR) [10]. The latest revision of the ILAR criteria was published in 2004 [1].

The development of the ILAR criteria for JIA involved combining, adjusting and building on existing criteria. The 'polyarticular' group was split into two distinct new categories based on a test for rheumatoid factor (RF), an autoantibody against immunoglobulin G (IgG) [11]. Patients who tested positive for RF tended to fare substantially worse than those who tested negative for this autoantibody [4]. In addition, patients with oligoarthritis were

initially split into two distinct disease categories based on whether they experienced persisting inflammation in fewer than five joints ('persistent oligoarthritis'), or whether the inflammation extended to five or greater joints ('extended oligoarthritis') after the first six months of disease. The patterns of joint involvement in the two oligoarticular categories were categorised into those involving i) only large joints, ii) only small joints, iii) large and small joints with predominating in upper limbs, iv) large and small joints predominating in lower limbs and v) large and small joints with no predominance. The initial classification criteria suggested that joint involvement patterns i) to iv) were common in both 'persistent' and 'extended' oligoarthritis, with group v) only present in the extended phenotype [10]. However, through further revisions of the criteria, the oligoarticular categories were combined into a single category, with joint patterns changed to descriptors, to aid the initial classification of JIA category within the first six months of disease. In addition, exclusions were later added to avoid the misclassification of patients with high probabilities of developing systemic, RF-positive polyarthritis, enthesitis-related or psoriatic JIA, which may all initially present with fewer than five inflamed joints [1].

Further additions to the ILAR criteria focused on these rarer disease categories. The EULAR classification criteria had sub-categorised patients into having a 'definite' or 'probable' diagnosis of systemic or psoriatic disease. The ILAR revisions removed the classification of systemic JIA for CYP who had experienced systemic features without arthritis, due to both the unfeasibility of continuing to monitor fever without providing antipyretics and the potential for infectious or malignant disorders with these clinical signs. Similarly, it was felt that a family history of psoriasis should be given equal weighting to the clinical signs of dactylitis or nail abnormalities, which were the distinguishing features between 'probable' and 'definite' psoriatic JIA . Therefore, a CYP can only currently be classified as 'having JIA' or 'not having JIA', with no 'probable' intermediate until further signs of disease have become established (Table 1).

**Table 1.** Classification of juvenile arthritis according to ACR, EULAR and ILAR criteria

| | ACR (1972)[8] | EULAR (1978)[9] | ILAR (1995)[1] |
|---|---|---|---|
| Juvenile arthritis classification | Juvenile Rheumatoid Arthritis (JRA) | Juvenile Chronic Arthritis (JCA) | Juvenile Idiopathic Arthritis (JIA) |
| Symptom duration before classification | 6 weeks | 3 months | 6 weeks |
| **Category definitions** | | | |
| Systemic arthritis | Definite: Arthritis accompanied by: <br>• Persistent intermittent fever (103°F or more daily) <br>Probable: <br>No arthritis: <br>• Fever <br>• Rheumatoid rash | Definite: Arthritis accompanied by: <br>• Fever <br>• Rash <br>Probable: <br>• No arthritis <br>• Fever <br>• Rash <br>• 2 of 3: <br>  o Generalised lymph node enlargement <br>  o Hepatomegaly or splenomegaly <br>  o Serositis | Arthritis preceded by fever that has persisted for at least two weeks <br>Fever has occurred daily for at least three days <br>Presentation with at least one of the following in addition to fever: <br>• Temporary erythematous rash <br>• Generalised enlargement of the lymph nodes <br>• Splenomegaly <br>• Hepatomegaly <br>• Serositis |
| Oligoarthritis | Arthritis affecting up to four joints. | Pauciarticular arthritis: Fewer than five joints affected at disease onset | Arthritis affecting under five joints in the six months following disease onset <br>Split into two subcategories: <br>**Persistent oligoarthritis:** <br>• Fewer than five joints are affected throughout the course of the disease <br>**Extended oligoarthritis:** <br>• At least five joints are affected after disease duration of six months |
| Polyarthritis | Arthritis affecting at least five joints | At least five joints affected at disease onset | **RF$^+$ polyarthritis:** <br>• Arthritis affecting at least five joints in the six months following disease onset <br>• A test for rheumatoid factor is positive <br>**RF$^-$ polyarthritis:** <br>• Arthritis affecting at least five joints in the six months following disease onset <br>• A test for rheumatoid factor is negative |

| Enthesitis-related arthritis | - | Juvenile ankylosing spondylitis (JAS): arthritis accompanies by enthesitis or sacroilitis<br><br>Arthritis with inflammatory bowel disease (IBD) | Arthritis accompanied by enthesitis<br><br>Or arthritis or enthesitis accompanied by at least two of:<br><br>• Currently suffering from or history of inflammatory lumbosacral pain and/or sacroiliac joint tenderness<br>• HLA-B27 antigen positive<br>• Onset in male CYP over the age of six<br>• Acute anterior uveitis<br>• History of first-degree relative suffering from enthesitis-related arthritis, ankylosing spondylitis, sacroilitis with IBD, acute anterior uveitis or Reiter's syndrome |
| Psoriatic arthritis | - | **Definite:**<br><br>Arthritis accompanied by typical psoriasis<br><br>Or arthritis accompanied by three of:<br><br>• Dactylitis<br>• Nail pitting<br>• Psoriasis-like rash<br>• Family history of psoriasis<br><br>**Probable:**<br><br>Arthritis and two of:<br><br>• Dactylitis<br>• Nail pitting<br>• Psoriasis-like rash<br>• Family history of psoriasis | Arthritis accompanies by psoriasis<br><br>Or arthritis accompanied by at least two of:<br><br>• Dactylitis<br>• Oncholysis or nail pitting<br>• Family history of psoriasis in a first-degree relative |
| Undifferentiated arthritis | - | Undefined arthritis | Arthritis that fulfils none of the criteria for other categories or criteria for more than one category |

ACR: American College of Rheumatology, EULAR: European League Against Rheumatism, ILAR: International League of Associations for Rheumatology, JRA: Juvenile rheumatoid arthritis, JCA: Juvenile chronic arthritis, JIA: Juvenile idiopathic arthritis, CYP: Children and young people, RF: Rheumatoid factor, JAS: Juvenile ankylosing spondylitis, IBD: Inflammatory bowel disease

There continues to be much debate about the current classification of JIA, with disease biomarkers such as anti-cyclic citrullinated peptide (anti-CCP), radiological findings and specific joint involvements not taken into account in the ILAR classification, all of which may potentially contribute to long term outcomes [12,13]. In addition, patients with persistent or extended oligoarthritis or RF-negative polyarthritis who have positive anti-nuclear antibody (ANA) tests have tended to have similar clinical characteristics [14,15], suggesting a grouping based on biomarkers rather than joint counts may exist. There is also mounting evidence that the systemic form of the disease should not be considered JIA at all, and constitutes a unique disease in its own right [16,17]. However, current epidemiological evidence and treatment strategies largely focus on the disease categories defined by ILAR[1].

### 2.1.2   A Common Comorbidity of JIA: Uveitis

In approximately 12% [18] to 30% of JIA cases [19], patients will develop uveitis: a usually asymptomatic inflammation of a structural component of the eye: the uvea [20]. Uveitis can present before or after JIA onset [21] and can affect one or both eyes [22]. Although the majority of patients do not experience any discomfort due to uveitis, it can quickly become sight-threatening in affected patients [22]. It is therefore essential that early access to ophthalmology and anti-uveitis medications are available. In the UK, the current standard recommendation is that all patients with suspected or confirmed diagnoses of JIA are referred to ophthalmology for screening [23]. Symptomatic patients or those with evidence of cataract or posterior synechiae are urgently screened within one week of referral; asymptomatic patients are screened as soon as possible but not longer than six weeks following this referral. Ongoing screening is then undertaken at regular intervals based on the age of JIA onset, ILAR category and ANA test results. Since younger patients, those testing positive for ANA and those with oligoarticular, psoriatic or enthesitis-related arthritis are at the highest risk [21], these patient groups are screened the most frequently [23,24].

### 2.1.3   Epidemiology of JIA

The estimated incidence and prevalence of JIA has varied between populations studied. A recent systematic review reported the global annual incidence of JIA at between 1.6 [25] and 23 [26] cases per 100,000 CYP, with a pooled annual incidence of 8.3 cases per 100,000 CYP [27]. The rates did not seem to be systematically higher or lower in any particular country or continent although the majority of populations studied were in Europe or North America [27]. Prevalence estimates had greater variation with between 3.8 [28] and 400 [29] cases per 100,000 CYP. The lowest of these estimates was from Eastern Asia and highest from Australia. Variation in incidence rates is likely affected by region-specific disease

classifications, environmental or genetic factors, or access to rheumatologists which might affect rates of diagnosis. Differences in how cases are ascertained for research purposes may also have affected these estimates, with more accurate representations likely from regions such as Scandinavia, where cases were identified at systematic health visits encompassing developmental checks, preventative care and immunisation [27]. In addition to these factors, prevalence estimates are likely affected by differing treatment regimens across continents and, since specific ILAR categories are associated with greater longevity of disease activity [5], distribution of ILAR categories. The specific drivers of the differences in both incidence and prevalence estimates across populations studied, however, cannot be truly disentangled due to the different designs across studied, with patient inclusion and exclusion criteria key to the eventual estimation of these parameters.

The most common category diagnosed, oligoarticular JIA, has an annual estimated incidence of 3.7 cases and prevalence of around 17 cases per 100,000 CYP [27]. The systemic form of the disease is relatively rare with a prevalence of 2.4 cases per 100,000 CYP and enthesitis-related and psoriatic JIA similarly at only 3.1 and 1.1 cases per 100,000 CYP, respectively [27]. In certain populations, enthesitis-related JIA has been reported as the most commonly-presenting onset type with 37% of CYP with JIA in this subgroup in Taiwan [30]. There is no current explanation for these differences, however, they are likely due to population differences rather than study design based upon the corroboratively high enthesitis-related JIA prevalence and relatively lower uveitis prevalence in Asian countries, such as India, Korea and Japan, compared with Western countries [30].

Whilst overall, JIA is known to more commonly affect females than males [27], specific ILAR categories are associated with differential gender distributions [4]. For the majority of categories, females are more likely to be affected with JIA; this can be up to three times more for oligoarticular and polyarticular JIA [31]. However, in systemic JIA, females and males may have equal risk of diagnosis [4], with the occurrence of enthesitis-related JIA in males far exceeding that of females [32]. In Taiwan, the incidence and prevalence of JIA in general has been reported higher in males than females [20] adding more evidence to the differential behaviour of the disease in this region.

### 2.1.4 Environmental Risk factors for JIA

Many factors have been studied as possible risk factors for JIA; however, associations have not always been very strong and much contradictory evidence exists. This section summarises some of the evidence surrounding environmental risk factors for JIA. It is also recognised that there is likely to be a genetic risk component to JIA [33], but this risk will not be discussed further within this thesis.

#### a) Prenatal environment

As the host of the foetus, maternal exposure and health play large roles in the development and postnatal outcomes of the unborn child. These exposures may be due to modifiable factors, such as smoking status, or unmodifiable factors, such as the blood groups of mother and baby. Few studies have focused on the risk of JIA with maternal factors, with no consistent associations reported between JIA and maternal age [34,35], maternal smoking [34-38] or non-tobacco air pollutants [39,40]. However, recall bias may be evident when focusing on maternal smoking. Given the evident risks of tobacco on multiple diseases such as cancers [41-43], cardiovascular, respiratory and musculoskeletal conditions such as rheumatoid arthritis (RA) [44-46], this association bears further investigation.

#### b) Birth Factors

CYP born via caesarean-section (C-section) may have poorer outcomes than those born through vaginal delivery [47-50]. One of the reasons cited for this association is the hygiene hypothesis, discussed below. In accordance, two studies have reported an increased risk of JIA in CYP born via C-section [35,50]. However, C-sections are often performed if there are higher risks of complications for either the child or mother in waiting for, or during the process of, vaginal-delivery birth [51]. It is therefore unclear if these increased risks of JIA reported are due to the mode of delivery or a factor more intrinsic to either baby or mother.

#### c) Postnatal Environment

**Breastfeeding**

Since breast feeding transfers essential immune materials to the infant [52], it may be expected that breastfed CYPs may be less susceptible to the future development of an immune-mediated disease such as JIA. There is mixed evidence for this potential association across four case-control studies of similar size, with no risk difference (n=2) [36,53] and higher risk of JIA in non-breastfed babies (n=2) [54,55] reported. Recall bias and recall accuracy potentially affected these cross-sectional studies that asked about past

breastfeeding. These may be particularly evident with longer follow-ups, with CYP in one study having JIA for up to ten years when their families were asked about the exact duration of breastfeeding [36]. Therefore, breastfeeding cannot be excluded as a risk factor for the development of JIA.

## *The Hygiene Hypothesis*

The hygiene hypothesis proposes that CYP who are more exposed, at a younger age, to potential pathogens have a boosted immune response because of early adaptive immunity [56]. It has been used to explain lower odds of developing JIA in CYP with siblings compared with only children in two small case-control studies [57,58]. Conversely two far larger studies have reported no associations between number of older siblings and JIA risk [35] and birth order in general and JIA risk [59], with these yielding more compelling conclusions due to the large sample sizes of over 3500 patients with JIA and 16500 controls combined [35,59]. Unlike breastfeeding, the exposure of sibling numbers should be fairly accurate and less prone to recall bias. However, no studies have focused on siblings and the risk of JIA from birth cohorts. Thus, selection bias may play a role in the types of CYP studied for this hypothesis.

## *Infections and Vaccinations*

Although the hygiene hypothesis may propose that CYP with greater exposure to pathogens in childhood may be at lower risk of JIA onset [60], an alternative proposed pathway to JIA onset is through early childhood infection [35]. In a prospective register in Sweden in over 3000 cases of JIA and over 13000 controls, 13% of patients with JIA had been hospitalised for any infection during the first year of life, compared with just 7% of the controls [35]. A seasonal effect has been observed [61], with JIA occurring in areas where outbreaks of particular viral or bacterial agents have been reported [62]. In addition, a dose-response association appears to be evident, with both greater numbers of hospitalisation for infections and a shorter time window following hospitalisation for infection associated with higher risk of JIA [63].

Although reports of associations between JIA onset and seasons or pathogen outbreaks may give credence to the theory of a viral pathogenicity to JIA onset, various studies have also demonstrated no association between early hospitalisation with infection and JIA risk [34], no association between rubella and JIA [64-66] and no difference in antibodies to parvovirus between JIA and healthy controls [67], with speculation that the presence of viral genomic DNA in patients with JIA may not be sufficient evidence of a viral mechanism to

disease onset [67]. It may be that i) only a subset of CYP are susceptible to JIA after infection, or ii) certain CYP are susceptible to both JIA and infection; there is no other mechanism between the two [68]. This latter theory has been proposed to explain the multiple studies associating earlier [68] and greater exposure to antibiotics [68-71] and later JIA onset, as well as exposure nearer to JIA onset [71].

### *Socioeconomic Status*

Socioeconomic status, which may describe education and skills, occupation, income, health deprivation, crime, barriers to key resources, living environments [72] or a combination of the above, is an independent predictor of health across multiple diseases [73,74]. Those with a lower socioeconomic status are more likely to have poorer living standards, working standards where employed, a greater number of chronic stressors in everyday life and poorer health literacy [75]. In JIA, this may translate to many factors mentioned in this passage, such as lower breastfeeding rates [76,77], greater tobacco smoke exposure [75], lower maternal age [78] and increased numbers of siblings for CYP born into more socially deprived families [79]. In concordance, a case-control study in 220 CYP with JIA reported that those from high-income families had twice the odds of JIA (95% CI 1.2, 3.1) [58]. However, this study did not adjust for maternal age, which may be both associated with income, number of CYP and the development of autoimmune conditions, as previously discussed, nor did it adjust for ethnicity.

### d) *Ethnicity*

The majority of studies focusing on the risk of JIA among people of different ethnic backgrounds have studied majority-Caucasian populations [60]. These studies generally under-represent ethnic minorities which has been attributed to a higher risk of JIA in people of European-descent [60,80,81]. This may be plausible given the lower JIA incidence and prevalence rates in majority non-Caucasian populations, such as Japan [82], Kuwait [83] and Oman [84], although relatively high prevalence estimates were gained from Egypt [85]. Differences in disease category risk may be evident among people with different ethnic heritages, with an overrepresentation of systemic JIA in India [86], RF-positive polyarthritis in those with black African, African American, Caribbean or Native American origins [80] and enthesitis-related JIA in Eastern Asian populations [30] and people of Eastern Asian descent [80]. That these categories are rarer forms of the disease and make up a larger proportion of all JIA cases in these populations may partially explain the lower incidence rates of JIA as a whole in these populations. However, there is evidence from studies in non-rheumatological conditions to suggest that, in majority-Caucasian populations, ethnic

minorities are underrepresented in research compared with the general population [87-89]. Thus, differences in susceptibility may not be due to differences in ethnicity, but instead differences in recruitment to research. This may be due to a lack of fluency in the given language of the majority-Caucasian population combined with limited access to translation services [89-92], a perceived stigma in participation or admission to having the condition studied [93-96], the overlooking of religious or cultural sensitivities [91,97] or logistical issues with attending the study appointments [90,91,98-101]. In addition, misconceptions from healthcare providers that patients from ethnic minorities might not wish to participate [102], may find communication difficult [102], might not understand the research [103] or might deviate from study protocol [104,105] have also been identified as barriers to recruiting this population subgroup.

## 2.2 The Treatment of JIA

There is no cure for JIA. The disease course is that of remission and relapse, with many CYP still experiencing symptoms of the disease into adulthood [7]. There are a number of pharmaceutical and non-pharmaceutical therapies aimed at helping patients with JIA achieve, and maintain, remission in addition to minimising the pain and disability associated with this disease. Given the heterogeneity of JIA, not all CYP will require all treatments. This section introduces the British Society for Paediatric and Adolescent Rheumatology (BSPAR) Standards of Care, discusses the main pharmacological and non-pharmacological interventions used in the treatment of JIA and discusses the approach to treatment of JIA.

### 2.2.1 Standards of Care

In the UK, standards of care, proposed by BSPAR, outline the minimum requirements of care for every young person affected with JIA [24].

The first consideration for effectively managing JIA is the prompt recognition of the condition in primary care and referral to specialist paediatric rheumatology services. The standards of care require that any CYP with suspected JIA should be seen by paediatric rheumatology within 10 weeks of symptom onset and within a maximum of four weeks following referral [24]. This is particularly important given a proposed 'window of opportunity' for effectively managing disease activity in JIA, discussed in a later section. The heterogeneity in the signs and symptoms of JIA require that, upon referral to paediatric rheumatology, every patient should have access to a multidisciplinary team. This team should include nine core team members, including professionals from paediatric rheumatology, ophthalmology, general practice and psychology. Additional support from

seven alternative specialties may be required if clinically indicated, including community nursing, play therapy, ophthalmology and orthopaedic surgery. Upon transition to adult care, an adult rheumatology specialist with experience in adult JIA must be provided. In addition to input from these specialties, patients and their guardians should take an active role in the management of the disease (Figure 2). This includes being provided with all necessary information to make informed choices and provide informed consent to any interventional therapies. This information must be age-appropriate and consider the impact of both their disease and treatments on their daily lives [24].
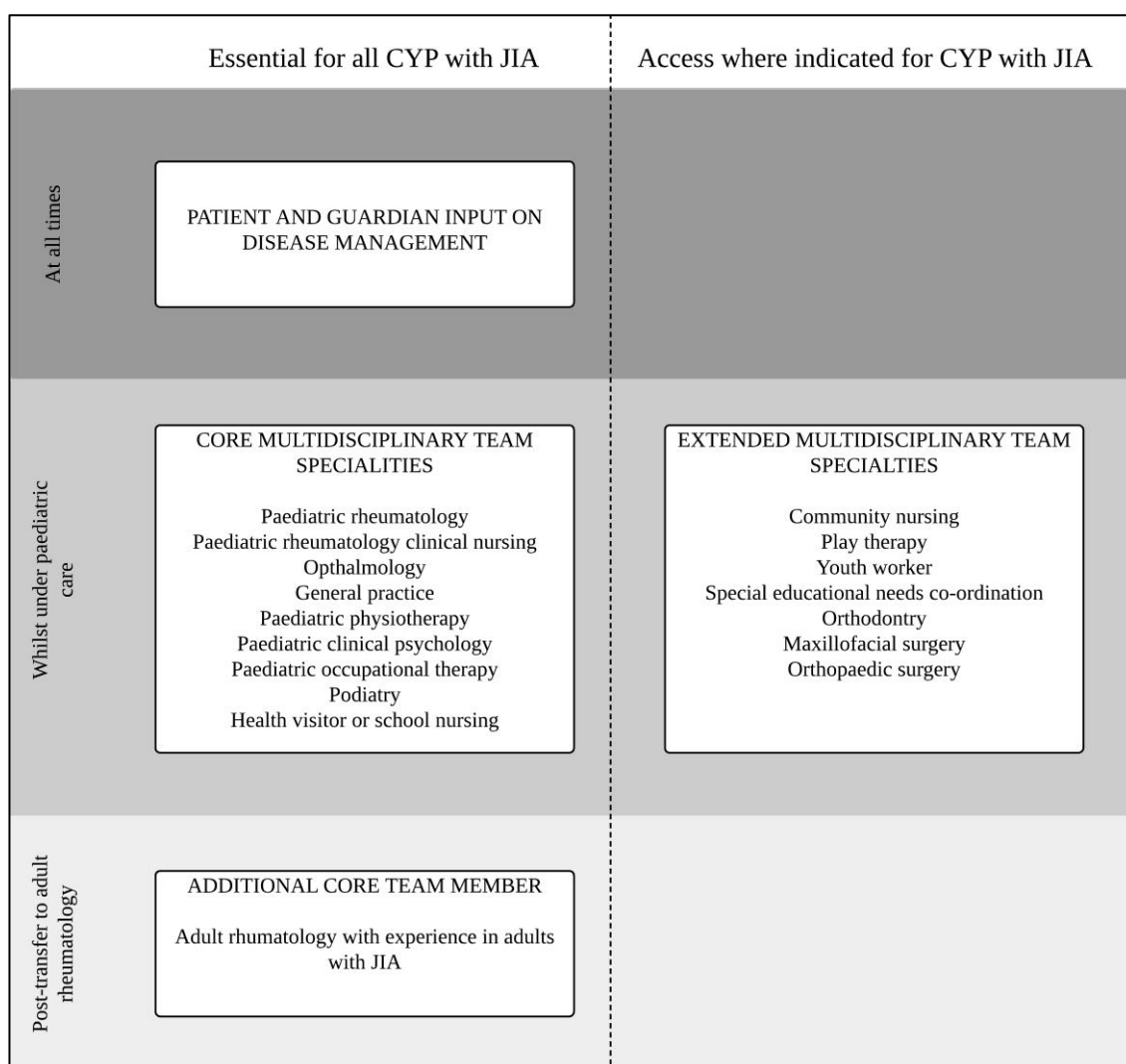


**Figure 2.** Members required for the care of patients with JIA. Adapted from Davies et al, 2010 [24].

Prompt access to treatment is required by the standards of care, administered, and where appropriate taught to be administered, by a paediatric specialist. Access to nitrous oxide, general anaesthesia and/or imaging technology should be provided if necessary when administering joint injections. In addition, to best control disease activity, and in some cases to monitor therapies, regular, frequent appointments with paediatric rheumatology

should be attended. The maximum limit for duration between appointments given by the BSPAR standards of care is four months for patients with active disease, with prompt access to further intermittent appointments available where required. In addition, a paediatric rheumatology nurse-manned telephone line for non-urgent queries is suggested [24].

The BSPAR standards of care for JIA are required to ensure consistent high-quality and multidisciplinary care for all young people with JIA in the UK. Whilst these standards provide frameworks for personnel and services that should be available, they do not give guidance on which specific therapeutics or the pathways for therapeutics should be provided for patients with JIA.

### 2.2.2 Pharmacological treatments for JIA

#### 2.2.2.1 Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a common first-line therapy for JIA due to their analgesic and mild anti-inflammatory properties [4] in addition to their high tolerance in CYP [106]. These drugs tend to suppress symptoms but have not been shown to stop, or 'modify', joint destruction [4]. To control JIA activity, further treatments are often necessary either in combination with, or in place of, NSAID therapy.

#### 2.2.2.2 Glucocorticoids

Glucocorticoid (or steroid) therapy may also be indicated for first-line use either as monotherapy or in combination with NSAIDs [107]. In the UK, according to the National Health Service (NHS) England treatment pathway for JIA, the initial treatment strategy for all CYP with JIA is similar: at diagnosis, all CYP should receive steroids [108]. These drugs are either administered directly into the affected joint via intra-articular injection or systemically via intra-venous infusion or oral administration [109]. The BSPAR standards of care require any steroid injections to be given within a maximum six week window following informed consent to the treatment [24]. However, a choice of intra-articular versus systemic steroid therapy may be based on ILAR category; CYP with lesser joint involvement (e.g. oligoarthritis) often receive intra-articular injections and those with polyarthritis systemic steroids. Those with systemic JIA or the other rarer ILAR categories may also receive systemic steroids to help control disease at initial presentation [108].

Steroids can be highly effective and have long-lasting effects [106], with one study reporting that 246 of 300 joints from a study population including patients of all JIA categories (n=61) experienced inactive joint disease for at least six months following intra-articular

steroids [110]. However, prolonged or repeated use of steroids is a concern due to adverse effects associated with these drugs, including growth failure, cushing-oid features and osteoporosis in the longer-term [4].

### 2.2.2.3 Conventional Synthetic Disease-modifying Anti-rheumatic Drugs

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) represent an important class of medicines for JIA. These are prescribed to not only control the symptoms of disease but also to modify the underlying disease process including the control of inflammation and subsequent joint damage. Methotrexate (MTX) is regarded the gold-standard csDMARD for JIA and is dosed according to the weight of the patient [4,111]. For some CYP with enthesitis-related JIA, an alternative csDMARD, sulfasalazine, is recommended [107]. However, in general, MTX is highly efficacious, with over 75% of patients having improvement and controlled disease progression after two years of treatment [106,112].

MTX is generally felt to be a safe drug. There is a concern regarding the possible toxic effects of this drug on the liver, though paediatric patients seem to be at lower risk of hepatotoxicity than adults with this medication [4]. More commonly, gastrointestinal side-effects, such as nausea, vomiting or diarrhoea, are experienced, affecting between 20% and 75% of patients [113,114]. Gastrointestinal side-effects appear to be ameliorated, in some cases, with the use of subcutaneous rather than the more common oral administrative approach, the use of antiemetics and behavioural therapies [111,114-116]. However, some CYP will also develop anticipatory nausea to MTX [116]. These side-effects may affect quality of life [117] and lead to non-adherence or even discontinuation of an otherwise effective therapy [114].

### 2.2.2.4 Biological Therapies

Biologic therapies are the newest development in the treatment of JIA [4,118]. The first biologic for JIA, etanercept, was licensed for this condition in Europe by the European Medicines Agency (EMA) in February 2000 [119]. It was accepted for NHS prescription in the UK for the polyarticular category in 2002 by the National Institute for Health and Care Excellence (NICE) [118]. Since then, further biologic agents have been licensed in Europe, including an additional anti-TNF therapy: adalimumab, an IL-1 antagonist: canakinumab, an IL-6 antagonist: tocilizumab and an anti-T-cell agent: abatacept for use in JIA [120]. However, due to their efficacy in RA and other conditions, additional biologics are often

used "off-licence" in CYP with JIA. These include the anti-TNF therapy infliximab, the IL-1 receptor antagonist anakinra and the anti-B-cell agent rituximab [121].

In the UK, biologic therapies are largely approved for use after MTX has been tried [108] (Figure 3). They are  often prescribed in combination with MTX to maximise efficacy [106]. The choice of biologic therapy is usually driven by clinical factors, including ILAR category and comorbidities, such as the presence of uveitis (where the first choice in UK practices is adalimumab or infliximab) or macrophage activation syndrome (first choice often anakinra instead of tocilizumab) [108,122].

Whilst biologic therapies have revolutionised treatment for patients who are refractory to csDMARDs, they come at a high price. The individual drugs cost on average (currently 2018) £5000 to £10,000 per annum [123].

### 2.2.2.5 Approach to the Pharmacological Treatment of JIA

JIA is a heterogeneous disease and not all CYP will require all therapies. It is generally accepted that CYP presenting with mild disease may only require NSAIDs, although research from the UK has reported that fewer than 10% will receive this therapy in isolation over the first three years following initial presentation to paediatric rheumatology [124]. In current practice, CYP with oligoarthritis are usually initially treated with IA steroid injections, only proceeding to MTX where joints remain active or multiple injections are repeatedly required. Those with polyarthritis are usually treated with MTX from the outset of disease, often in combination with steroids. These patients may be escalated to biologic therapies if refractory or cannot tolerate MTX [124]. Until recently, no specific treatment guidelines existed in the UK. However, the increasing choice of biologic therapies prompted NHS England to publish treatment pathways in 2015 to fill this gap [108] (Figure 3).
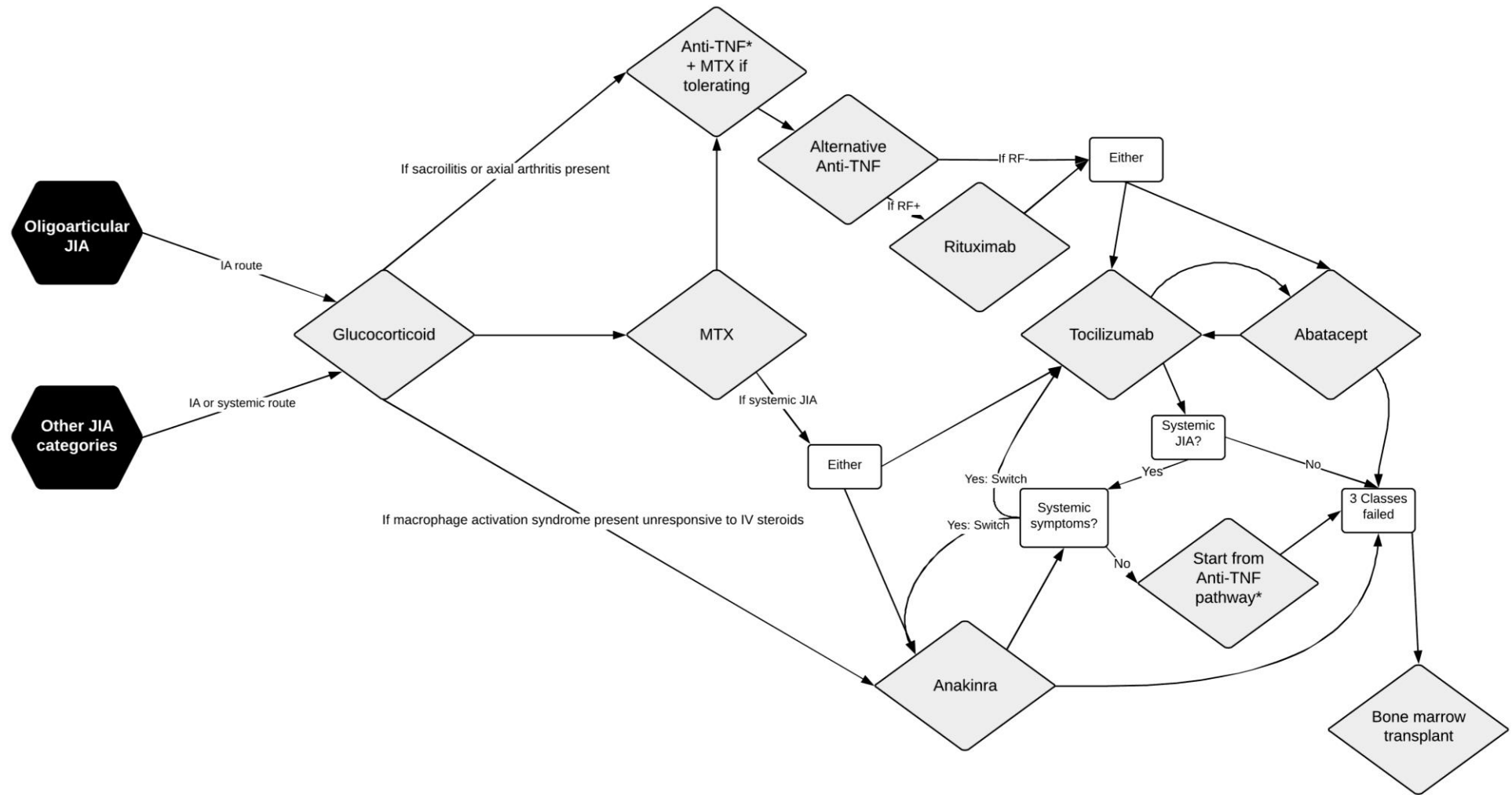
**Figure 3.** Treatment pathways for patients with JIA in the UK. Adapted from NHS England interim policy statement [108].

### 2.2.3 Non-Pharmacological Treatment of JIA

In addition to pharmacological interventions, many patients also benefit from non-pharmacological interventions such as psychological interventions or physical therapy. These interventions are also important to control disease activity, improve symptoms and promote rehabilitation and well-being in JIA.

#### 2.2.3.1 The Treatment of Pain

One of the principal symptoms of JIA is pain [125]. However, there are no current guidelines for the management of either acute or chronic pain in JIA [125]. Pain can be associated with inflammation and therefore controlled using anti-inflammatory medication previously discussed. Principally, this is using NSAID therapies principally, which have analgesic properties [125,126], with evidence that DMARDs may also reduce pain [127-129]. Many patients, however, develop chronic pain that persists despite the absence of active joints and raised inflammatory biomarkers or tissue damage [125,130], with between 40 to 90% of CYP reporting pain even years after the initiation of anti-rheumatic therapies [131,132]. Whilst ongoing pain in CYP may be temporarily controlled using opiates [133], there is discomfort among healthcare professionals about using these therapies in young people over a sustained period of time, particularly with regard to dependence and ongoing side-effects [134]. However, since chronic pain in JIA is multifactorial and associated with many other factors, including sleep, functional ability, health-related quality of life and fatigue [135-137], CYP with JIA and chronic pain require a multi-disciplinary approach that extends beyond pain medications [24], such as physical, sleep and psychological therapies [125], discussed here.

#### 2.2.3.2 Physical and Occupational Therapies

To aid recovery and maintain functional ability in affected joints as well as address the biological processes of pain, all patients are recommended some form of physical therapy for their JIA [24]. These are particularly important given that CYP with JIA tend to be less physically active than their contemporaries, which may lead to muscle de-conditioning and therefore additional disability and pain [138,139]. Therapies targeting functional ability include physical, occupational and self-management interventions [140]. The aims of these therapies may be to restore mobility, improve stability or improve pain management. Techniques to relax muscles and surrounding joints may include the use of hot packs, heated pools or baths before joint mobilisation or manipulation [4]. This joint mobilisation involves the passive movement of the joint to anatomically correct positions. Cold temperatures may be used to reduce inflammation and aid in the mobilisation techniques [4]. Conversely to relaxation techniques, exercise programmes may also aid in the range of motion of

affected joints alongside reductions in pain [141-143]. Whilst the previously mentioned techniques aid in generic pain management and mobility, occupational therapy provides the CYP with exercises and aids to cope with specific tasks in everyday life. Occupational therapists may provide the CYP with techniques or assistive tools such as pencil grips and walking aids [4]. The benefits from the previously mentioned interventions can be experienced in the short-term and may help the patient regain their normal activities. However, other functional therapies, such as splinting and traction, aim to prevent poor long-term outcomes, such as deformities from subluxation and ankyloses [4]. Whilst these interventions may substantially improve function and/or pain for CYP with JIA, they do not address the psychological or psychosocial aspects of JIA morbidity that is not mediated through biological processes.

### *2.2.3.3 Psychological Therapies*

Access to psychological services is generally poor for CYP with JIA [125], with increasing development of internet-based therapies to aid pain management in the absence of psychology referrals [125,144,145]. For CYP with JIA and chronic pain, psychology professionals can provide counselling and education on self-management techniques [125]. These techniques focus on two fronts: i) modifying behaviour of the CYP to better cope with their pain and ii) modifying the CYP's experience of pain when it arises. To these ends, cognitive behavioural therapy, which focuses on both short and longer-term self-management of pain, has proved successful for many CYP with chronic pain [146,147] including those with JIA [148,149]. It is at these clinics, and those with occupational therapists, that the link between sleep and pain can be adequately addressed, although the direction of this relationship is unclear [125].

### *2.2.3.4 Surgical Interventions*

For patients experiencing more severe symptoms where the therapies outlined above have not adequately controlled disease activity and/or pain, synovectomy or reconstructive surgeries may be appropriate. These more extreme interventions may be targeted at preventing progressive synovitis and joint erosions, or restoring function if damage is irreparable [4]. Difficulties with skeletal growth in CYP with JIA must be taken into account when considering surgical procedures affecting joints [4]. An initial form of surgery, with the aim of suppressing inflammation, is synovectomy. This involves the removal of synovial membrane that has become inflamed [4]. However, due to the size of the instruments and difficulties in rehabilitating younger CYP, this form of surgery is not indicated for CYP with JIA under the age of six years [4].

Where joints have eroded or there is evidence of deformity, synovectomy may no longer be a viable option to restore joint function. In these cases, reconstructive surgery may be the final option to restore function and reduce pain associated with disease [4], including osteotomy, arthrodesis and total arthroplasties, although total arthroplasties are relatively rare in JIA [130,150].

### 2.2.4 Treatments for Uveitis

The treatment of uveitis is in parallel with that of arthritis. If uveitis is detected upon screening, treatments for the acute stages initially include a combination of topical and systemic steroids to reduce inflammation in addition to therapies to prevent adhesions within the affected structures [151]. If the uveitis becomes chronic, the treatment pathways are similar to those observed for joint-specific inflammation in JIA. Namely, progression to MTX and then combination therapy with a biologic agent [22]. As treatment pathways for joint-specific inflammation differ across ILAR categories, the choice of treatment when both arthritis and uveitis are present usually reflects the highest level of treatment required to control both manifestations (e.g. if MTX controls joint activity but not uveitis, a biologic therapy may be considered).

### 2.2.5 Goals of Therapy and Treating to Target

The goal of treatment of JIA is remission; however, there are currently no agreed measures of remission for use in clinical practice to use as therapy targets [152]. For example, no specific definition or measure of remission has been incorporated into the current NHS England pathway for JIA [108] to assist treatment decisions .

In RA, treat to target (T2T) strategies have been proposed, studied in clinical trials and introduced into clinical practice[153,154]. T2T involves defining a target disease state (e.g. remission) and at scheduled interval assessments (e.g. monthly), it is determined whether the patient has achieved that disease state. If the state has not been achieved, treatments are escalated until the target state has been achieved. This could involve a combination of increasing doses of existing therapies and/or switching to an alternative therapy (Figure 4) [154].
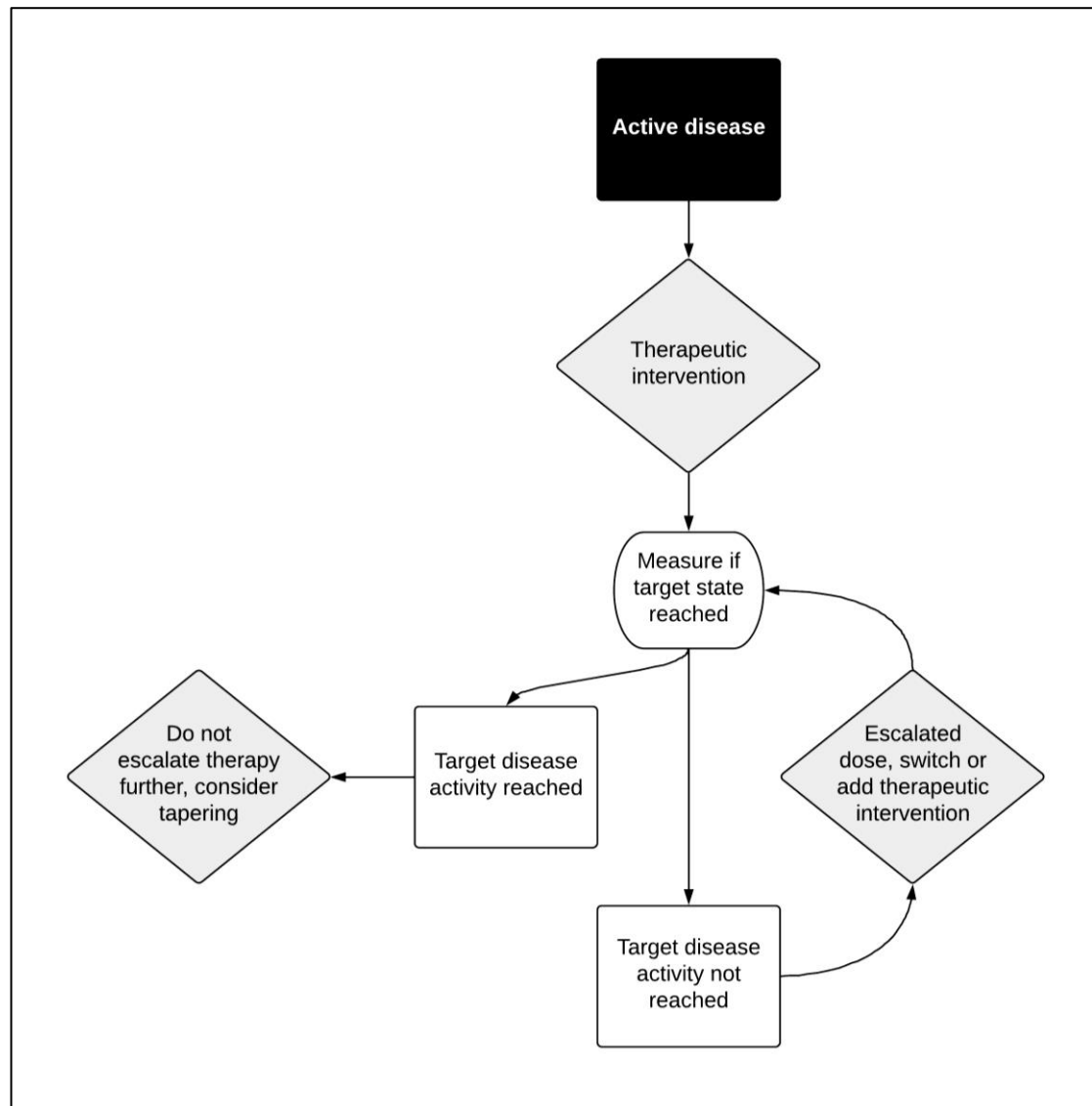
**Figure 4.** Basic framework for a treat to target strategy in inflammatory arthritis

T2T strategies have not yet been tested or implemented in JIA. Several publications have proposed these strategies on the back of evidence in RA [152,155-158]. However, treatments differ between RA and JIA, with JIA being a much more heterogeneous condition than RA. Therefore, it is unclear whether this strategy will be as successful, or acceptable, in JIA. In addition, it is unclear what the treatment target state should be for JIA. A vast number of possible outcomes exist for monitoring disease in JIA. Similarly, several composite outcome scores, discussed in a later section, have been developed although many are not yet routinely used in clinical practice.

### 2.2.6 Summary: Treatments for JIA

Many pharmacological and non-pharmacological therapies are available for JIA. Broad treatment guidelines exist which take on escalation strategies, where CYP are progressively moved forward to more aggressive and/or targeted therapies once failing

initial treatments. The current UK guidelines largely focus on pharmacological management [108]. Although non-pharmacological management is included in the BSPAR Standards of Care [24], specific guidelines for when and how to integrate these practices have not been published. In addition, the many symptoms of JIA that may require non-pharmacological therapies have not been addressed. The aims of treating the signs and symptoms of JIA are to improve short and long-term outcomes. With an increasing choice of therapies, the concept of precision medicine in JIA is attractive. To be able to truly incorporate precision medicine into treatment guidelines, initial features of disease and outcomes over the short and long-term should be considered. To understand if an intervention is successful in a group of patients or whether a different approach is warranted, consistent measurement of outcomes is necessary. This requires the development of outcome measures that are applicable across the spectrum of patients with JIA, who may differ physically, emotionally and sociologically. The next section will discuss the outcome measures currently in use for JIA.

## 2.3 Outcome Measures in JIA

There is no single gold standard measure for assessing disease activity in JIA. The disease symptoms are driven by underlying inflammation in the joints and other tissues or organs and within this heterogeneous disease, the manifestations of active disease can be diverse and can include patient symptoms (such as pain, fatigue), physical signs of disease (such as joint swelling) as well as biological abnormalities (such as raised serum inflammatory markers) [4].

Traditionally, the physical signs of disease, including abnormal biomarkers, have been used in clinical practice as a basis for pharmacological treatment decisions, specifically in terms of steroid and DMARD therapies [107]. Patient-reported symptoms may be considered contentious to use for this purpose due to i) Not being specific targets for therapeutics and ii) Possibly not relating entirely to JIA [159]. However, these non-inflammatory outcomes offer an insight into the impact of the disease on patients' everyday lives in addition to being potentially useful contributors to both pharmacological and non-pharmacological treatment decisions [159]. To be able to monitor, communicate and act on any feature of disease, standardised outcome measures are required.

Disease outcome measures in any condition are used for the primary purpose of standardised monitoring of disease as well as outcomes in clinical studies. These measures can assess a wide range of outcomes, from purely clinical outcomes that must be measured in a clinical setting e.g. blood biomarkers, to outcomes that may be outside of

direct clinical control but have great impact on a patient's everyday life e.g. wellbeing [160]. As previously mentioned, the standardised use of outcomes measures is vital. This initially allows clinicians to assess and communicate both current disease status and prognoses to patients. Both parties can then make informed decisions regarding future treatment strategies. In addition, the standardised use of outcome measures in clinical research facilitates the monitoring and recording of disease across larger cohorts of patients in a standardised fashion in order to facilitate direct comparisons of treatment efficacy (or effectiveness) across study settings [161].

### 2.3.1   Development of an Outcome Measure: the Delphi Process and Nominal Group Technique

The Delphi process and Nominal Group Technique (NGT) [162] are often used in the development of outcome measures in addition to the creation of core data sets or combining expert opinion for other purposes.  These often follow initial focus groups with a range of stakeholders, including patients and carers, healthcare professionals and researchers [163,164]. These qualitative sessions allow the exploration of the need for outcome measures and the importance of different outcomes to the various stakeholders. This should lead to greater confidence in the completeness of the initial long-list of potential outcomes for consideration as part of a Delphi or NGT process [163].

*Combining Expert Opinion: The Delphi Process*

The Delphi process encompasses the completion of iterative questionnaires by an initially remote respondent group (academics/healthcare professionals/patients/carers) who then meet to consolidate generated ideas. The goal of this process is to combine expert opinion in a consensus-based manner by first generating a long-list of potential items for core outcome sets, questionnaires or composite outcome measures [162,165]. This list is eventually condensed through multiple rounds of anonymised voting regarding items to include or exclude from the core outcome set, questionnaire or composite outcome criteria [162]. Whilst in practice, there are multiple methods of completing a Delphi process, the same iterative structure can allow the collation of opinions from experts across multiple areas into the development of such resources. This may be independent of, or in combination with, statistical techniques to validate new outcome definitions against existing measures [161].

*Combining Expert Opinion: Nominal Group Technique*

Nominal group technique (NGT) is similar to the Delphi process in that consensus opinion is sought from experts. However, there are substantial differences between the two

processes. Unlike Delphi, the NGT process is always set within a face to face meeting. Generation of ideas, like Delphi, are initially completed independently. This takes place silently in a face-to-face meeting, with each respondent generating ideas, for example a list of potential items to include in a core outcome set or composite measure. Each respondent then reads out one idea in turn until no further components are raised. At this stage, either the same group or a new group of experts feeds back on each idea raised, with discussion to focus on clarifying the meaning of each item and evaluating whether the item is suitable for inclusion. Voting is then completed to form a consensus on which items to include in the final outcome set or measure [162].

The NGT process may build upon results from a Delphi process, with experts joined in a face-to-face setting once the selection of measures to include has been completed. In this setting, NGT could be valuable in deciding how the single outcomes selected should be combined or scored for the final composite measure [161]. In addition, these groups could come to consensus on how to test the utility of the completed measure [165], again with or without statistical input [161]. However, both Delphi and NGT methods have limitations which may restrict their utility in the development of core outcome sets or outcome measures.

### *Limitations of Delphi and Nominal Group Techniques*

The Delphi and Nominal Group Technique processes are excellent methods to combine judgement from multiple sources of individual experts. These are particularly helpful in exploring the underlying assumptions driving respondent judgement and to synthesise informed judgement on a given topic [162]. However, for the creation of core outcome sets and outcome measures, they have limitations both in theory and in practice. The theories of both processes rely on expert judgement being the best available evidence to answer a specific question. However, all forms of expert judgement are prone to biases such as confirmation bias, selection bias, small samples sizes from which opinions are formed and the lack of control for confounding factors [166]. In summarising the effectiveness or safety of particular therapies, expert opinion, gained through anecdotal evidence, is deemed by NICE to be a 'very low' quality form of evidence [167] and lies near the bottom of evidence hierarchies [166]. This may also apply to the development of core outcome sets or measures where any form of published evidence available in human participants regarding the capture of specific disease constructs or prediction of outcome by measures of disease may be appropriately deemed better quality evidence than expert opinion. In theory, experts from a range of sources, such as physicians and allied healthcare professionals, researchers

in the field and patients and carers, would form the respondent group. This would allow the different users of the questionnaire or outcome measure to influence which items are most important from their perspective, the reasoning behind their choices and potential issues surrounding feasibility. However, in practice, Delphi processes have traditionally been dominated by physicians [161,165,168], with changes in more recent years moving toward the greater inclusion of the patient/carer viewpoint [169-171]. Even when limiting the respondent group to physicians only, the results of the Delphi process will only have internal validity within this small group. Further opinion is often not sought from external potential respondents [162] and thus the generalisability of expert opinion gained through a Delphi process is limited. When meeting face to face, dominant personalities may skew consensus results. In addition, the hierarchy within the profession may lead some individuals to agree with more senior experts, against their own judgement. Finally, the process of providing feedback between sequential questionnaires has been reported to influence the results of the subsequent questionnaire [172]. Scheibe et al [173] provided false feedback to respondents and reasoned that one of the following three options would be taken in response to this feedback i) The feedback would be ignored, ii) The feedback would be rebelled against by voting more extremely to influence the results to their view and iii) The feedback would be conformed to. The third option was taken most frequently [173], thus even the internal validity of results from Delphi or NGT processes is questionable.

### *Statistical Approaches to Core Outcome Set or Outcome Measure Development*

An alternative or complementary approach to consensus-based techniques for core outcome variables (COVs) or outcome measure development is through statistical means. This can be completed where current evidence or single outcome measures exist regarding the capture of specific disease constructs of interest. Following the selection of an initial long-list of items to include, short-listing and developing the final core set or composite measure may take a stepwise or comparative approach, with different forms of the final set tested against existing measures. This could take the form of stepwise regression, item response theory analyses or testing receiver operating characteristics [174]. Whilst consensus-based methods incorporate items important to the parties invited to participate, statistical methods may develop a measure that more accurately represents the construct of interest [175] without the biases involved in anecdotal evidence. Care should be taken that the models developed are feasible to implement in the desired setting [176] and validation methods of acceptability, discriminant abilities between different states of the construct and future outcomes, reliability and feasibility should be tested as with those developed under consensus-based techniques.

## 2.3.2 Development of an Outcome Measure: Outcome Validation

Once a core outcome set or measure has been created, it should be tested to determine different elements of applicability, or 'validity'. Capture or achievement of the outcome in question may differ depending on the investigator, patient or disease characteristics in different populations. In addition, whilst the core set or outcome measure may have seemed reasonable to the respondents in Delphi/NGT processes, it may not be seen to capture all important elements of the underlying construct. However, where important elements are captured, they must also be deemed clinically feasible to implement. For these reasons, new outcome measures should undergo a validation process.

Several international groups have aimed to improve the development and reporting of outcome measures, such as the Core Outcome Measures in Effectiveness Trials (COMET) [177], Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) [178] and the Patient-Centred Outcomes Research Initiative (PCORI) [179]. Specific to rheumatology, Outcome Measures in Rheumatology (OMERACT) have produced a development and validation guide for core outcome sets and measures, which, although intended for use in clinical trials, are widely available for application by research investigators outside of this team in observational research [180]. Overall, the measurement properties of the instruments should be of a high standard and fulfil several criteria (Table 2).

Outcome measures should, firstly, truly measure the construct that they intend to capture. This can be assessed through face and content validities in conversations with patient groups and other stakeholders. Outcome measures should also be able to discriminate between different severities of the outcome at a static state and over time. These comprise construct and criterion validities, assessed through comparison to other measures of the same construct [180,181]. However, these validities are concerned principally with the sensitivity of the outcome measure in question: Does this outcome measure capture a disease state in patients who are truly affected by the state in question? They do not assess the specificity of the outcome measure: whether people who do not have the disease state are identified as such. Classification and responsiveness validities therefore not only assess whether patients are accurately classified into construct groups, but whether these groups are clinically meaningful. In addition, reliability requires the production of consistent scores when measured by different investigators across different recipients, measured using inter-rater and test re-test reliabilities [180,181]. Finally, feasibility validation is concerned with whether it is appropriate to use the outcome measure in practice when

knowledge of the outcome would be clinically useful. This is multifactorial and takes health economics, time and ease of completion and any potential risks to the target population into account [180,181] (Table 2).

The types of validation and reliability assessments described are vital to ensure the applicability of outcome measures. When outcome measures accurately capture static states and clinically important changes across samples of patients in which they were developed, these are said to have 'internal validity'. However, to be truly generalisable, a measure should be able to demonstrate sufficient accuracy, reliability and feasibility in a population external to that it was created in: external validity.

**Table 2.** Validation processes

| Validation type | Description | Potential tests of validity |
|---|---|---|
| Face validity | Whether the outcome components seem reasonable to the target population | Qualitative assessments by service users and providers |
| Content validity | i) Whether the most important aspects of the outcome, according to the target population, are being captured<br>ii) Whether each component captures a distinct element of the construct<br>iii) Whether the format of the test is acceptable to capture each element of the construct | Qualitative assessments by service users and providers |
| Construct validity | Whether the outcome converges or diverges from other measures of the same construct | Pearson's or Spearman's correlations [182]<br><br>0.0 to (-)0.3: Negligible<br>(-)0.3 to (-)0.5: Low<br>(-)0.5 to (-)0.7: Moderate<br>(-)0.7 to (-) 0.9: High<br>(-)0.9 to (-)1.0: Very high |
| Criterion validity | Whether patients with the same construct are classified similarly using a gold standard (sensitivity) | Sensitivity of $\leq 0.5$ no better than chance. Approaching 1.0 has perfect sensitivity [183] |
| Classification | i) Whether the measure can discriminate between patients with and without the construct of interest<br>ii) Whether the measure can discriminate between clinically-relevant construct states in terms of prognosis | Specificity of $\leq 0.5$ no better than chance. Approaching 1.0 has perfect specificity [183]<br>Longitudinal analyses for prognoses. |
| Responsiveness | Whether the measure is sensitive to change in the underlying construct | |
| Reliability | i) Whether the measure similarly classifies patients where the construct has not changed<br>ii) Whether the measure classifies patients into similar construct categories between investigators | Intra-class correlation coefficient (ICC) [184]:<br>$\leq 0.5$: Poor reliability<br>0.5 to 0.75: Moderate reliability<br>0.75 to 0.9: Good reliability<br>0.9 to 1.0: Excellent reliability<br><br>Cohen's Kappa:<br><0.0: Poor agreement<br>0.0-0.4: Slight to fair agreement<br>0.4 to 0.6: Moderate agreement<br>0.6 to 1.0: Substantial agreement |
| Feasibility | Whether it is appropriate to use the outcome measure where knowledge of the construct is clinically useful. Incorporates:<br>i) Health economics<br>ii) Time to train and complete<br>iii) Ease of completion<br>iv) Potential risks to the target population | Qualitative interviews with service users and providers<br>Health economic analyses |

ICC: Intra-class correlation coefficient

The various outcome measures currently in use for JIA have not undergone every process in the validation pathway and many, including the core outcome set, were published before recommendations by OMERACT had been published. However, the majority used routinely in clinical practice and/or research have undergone at least partial validation under the methods described. Challenges have arisen in multiple areas. One of the main issues is that gold standards outcomes are rare in JIA. In accordance, new outcome measures would not need to be developed if an adequate, feasible and affordable gold standard was already in common practice. In these situations, 'concurrent validity' has been substituted for criterion validity in order to assess whether similar CYP are identified by measures designed to measure the same construct e.g. against other measures of the same construct or disease process [181]. The components of the outcome measures are tested occasionally for face validity, but rarely in the true target population. Many outcome criteria have only been tested for face and content validity by target investigators, i.e. healthcare professionals, rather than the target recipients themselves [161,165,168,185,186]. One of the other major issues surrounds feasibility of testing; when diseases are rare, fewer and smaller patient groups are available for both internal and external validation of outcome measures. In addition, testing a new measure that may be vital for understanding the JIA disease process takes time for clinicians to learn and even more time to incorporate into their busy clinics. For this reason, retrospective datasets or data from existing clinical trials are often used as an easily accessible source of data to test both internal and external validity [168,181,187]. Selection bias in these cases may play a role in the non-applicability of some outcome measures in the general clinic population. Despite these issues, there are a set of core outcome variables that are routinely collected in JIA [161]. The combinations of these single items into composite outcome criteria may yield improved assessment of JIA for both clinical and research purposes.

### 2.3.3 Single versus Composite Outcome Measures in JIA

Single outcome measures for JIA capture individual disease features. This may include the measurement of a single item, such as the number of active joints, or multiple items within a single outcome measure, such as multiple areas of function for a total functional ability score. These are valuable to assess the current state of disease activity and/or the impact of disease on a patient's daily life. Single outcome measures may therefore prompt the consideration of specific treatment pathways by paediatric rheumatologists, such as DMARD therapy for joint inflammation, as indicated by a high active joint count, or referral to physiotherapy for poor functional ability [4], as measured by the Childhood Health Assessment Questionnaire (CHAQ) [188]. However, considering each measure in

isolation does not provide a complete picture of the disease or its impact on a given CYP. Composite outcome measures have therefore been developed, combining single outcome measures into scores or classification criteria to capture multiple elements of disease in a single measure.

### 2.3.4    Single Outcome Measures in JIA

#### 2.3.4.1 Core Outcome Variables in JIA

There are many potential measures of outcome in JIA. However, in 1997, in response to the lack of consistent outcome reporting across clinical trials in JIA, Giannini et al. proposed a combination of COVs for this disease [157,161]. The selection of outcomes to include in the core set was completed using a Delphi process among a group of physicians. No patients or allied healthcare professionals were included. In brief, clinical experiences of the group of physicians were used to condense a long-list of outcomes that had already been used in clinical trials to a short-list and then to the final core outcome set for JIA, which included six measures (Box 1) [161]:

---

**Active joint count**

**Limited joint count**

**Erythrocyte sedimentation rate (ESR)**

**Physician's global assessment**

**Parental global assessment**

**Functional ability (using the Childhood Health Assessment Questionnaire: CHAQ)**

---

**Box 1.** The Core Outcome Variables for JIA, as defined by Giannini et al [161]

*Active and Limited Joint Counts*

Active joints are defined as swollen joints not caused by underlying deformity or joints with limitation of motion in addition to tenderness, pain or heat [8,189]. These are considered one of the cardinal signs of JIA and contribute to the diagnosis and disease classification, felt to be a key manifestation of joint inflammation. Following periods of low disease or clinically inactive disease (CID), active joints may be one of the primary signs of a disease flare [190].

In contrast to the swelling, heat and/or tenderness associated with active joints, joint limitations may be evident in the absence of these features [165,191,192]. Joint range of motion

may improve over time with effective anti-rheumatic therapies [192] but may persist in CID due to structural changes as a result of previous inflammatory disease activity [191].

### ESR

As an acute phase reactant, erythrocyte sedimentation rate (ESR) is considered an objective biomarker of inflammation [157]. It is measured by recording the speed of sedimentation of aggregated erythrocytes in blood plasma, with higher values indicative of inflammation [193,194]. ESR values correlate only moderately with other features of disease, flare of disease and its impact in CYP with JIA [190,195]. This may be due to ESR capturing a unique aspect of JIA not observable through other means of observation, or the capturing of inflammation due to causes other than JIA. Since ESR is a generic marker for inflammation [157], raised ESR observed in clinically inactive disease [196] may indicate underlying persistent activity or may be raised for reasons unrelated to JIA, such as infection, renal disease or obesity [197]. Another limitation is that in attaining a value for ESR, blood must be taken. This procedure is often stressful, particularly in younger CYP [157], and may not be considered routine in CYP with milder disease, or those not on medications, such as MTX, that require blood monitoring [198].

### Physician's Global Assessment of Disease Activity

Most frequently scored on a 100mm visual analogue scale (VAS) [157], or alternatively using Likert scales with interval scores [199] or ordinal measures [161,200], the physician's global assessment is intended to give an overall picture of the physician's opinion of disease activity in JIA [157]. The anchors at each end of the 100mm VAS are 'no activity' (at 0mm) and 'maximum activity' (100mm) [160]. There is currently no standardised method for which manifestations of disease or test results physicians should consider when scoring or what level of disease each value on the scale represents. This has led to some variability in the score among children and adults with perceivably similar disease states or within the same patient when assessed by two physicians [201,202].

The physician's global assessment is driven by features of disease observable or reported by patients at clinical appointments. It may therefore not encapsulate features of disease experienced outside of clinical appointment or the impact of disease on the patient. This score has been previously reported to correlate strongly with features of inflammation, such as joint count, and is highly responsive to changes in disease activity, but is less highly correlated with patient-reported outcomes such as pain [199].

## Patient/Parent Global Assessment of Wellbeing

The patient/parent global assessment of wellbeing is similarly scored on a 100mm VAS. This measure is intended to give an overall picture of wellbeing rather than disease activity from the point of view of the patient rather than the physician [157]. Therefore, the anchor at 0mm represents 'very good' wellbeing with a score of 100mm representing 'very poor' wellbeing [160]. This measure correlates with, and is moderately responsive against, other features of disease activity [203,204]. Where physicians' and parents' global scores have been reported discordant, physicians tended to score higher than parents in the presence of active joints and parents scored higher than physicians in the presence of greater pain and/or functional disability [160]. These global scores therefore likely capture different constructs and are both necessary to monitor the full impact of JIA on a given CYP.

## The Childhood Health Assessment Questionnaire

The final core outcome criterion in Giannini et al.'s core outcome variable set is functional ability [161]. Although multiple tools and measures have been developed for assessment of functional ability in CYP with and without JIA [205-210], the most commonly used measure in JIA is the CHAQ [188]. No formal statistical or Delphi procedures were undertaken to develop the questionnaire. Instead, a single study group derived and adapted this questionnaire from the Stanford Health Assessment Questionnaire (HAQ), which assessed functional ability in adults with RA [211]. Both the CHAQ and the HAQ comprise eight domains of function: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. These are designed to cover the extent of activities that can be expected to be completed by a healthy person on a daily basis. In addition, sections on aids and devices, including the need for help from another person, are available for each domain.

There are four possible options for each question within the eight domains on the HAQ, ranging from 'without any difficulty' to 'unable to do' (scored between zero and three, respectively) [211]. A fifth, 'not applicable', option was added to the CHAQ for young CYP who cannot be expected to complete certain tasks due to their age, for example 'do household chores'. The highest score for any question within each domain then represents the domain-specific score. If help from an aid, device or person was needed for a particular domain, the domain-specific score is changed to '2' if below this value using the domain-specific questions alone. The domain specific scores are then summed to produce a score out of 24, then divided by eight to give a final score (0 to 3). Higher final scores therefore represent poorer functional ability [188,211].

Other modifications of the CHAQ from the HAQ include the addition of activities applicable to a younger audience, such as 'writing or scribbling with a pencil' in the 'grip' domain, which had previously only asked about car doors, jars and taps [188]. In addition, certain questions were rephrased for a younger audience: The HAQ question regarding 'reaching…a 5lb object (e.g. a bag of potatoes)' was adapted to 'reach…a heavy object such as a large game or books'. Finally, where the HAQ was to be self-completed, the CHAQ is designed for proxy completion. Thus, the questions have been reworded from the first to third person (e.g. 'can you' versus 'can your child') [188,211].

Although it is possible to achieve scores along the entire scale from 0 to 3 on the CHAQ, it has a known flooring effect where scores cluster near zero [212]. In relation to this phenomenon, CHAQ scores are poorly [204,213] to moderately [214,215] responsive to changes in the disease over time, with limited ability to detect improvements in CYP with mild disability [216]. However, the CHAQ has been reported to be highly reliable, is relatively quick to complete and has been translated into many languages for use worldwide [217].

### 2.3.4.2 Other Outcomes in JIA

Although the COVs, as previously discussed, encompass objective and subjective measures of disease activity in addition to the impact of the disease on function and wellbeing, several additional outcomes are assessed regularly in JIA. This section summarises the main other outcomes which will be used and/or discussed in later sections of this thesis.

### CRP

Similar to ESR, C-reactive protein (CRP) level is an acute phase reactant and therefore elevated results of this test represent systemic rather than cause-specific inflammation [185]. The choice of ESR rather than CRP as the acute phase reactant to include in the COV set likely relates to the date of development of the core outcome set, which predated the widespread use of CRP in clinical practice. In addition, unlike ESR, different assays for CRP have different cut-points for 'increased' values. However, there is high correlation with active disease for both CRP and ESR [218].

### Morning Stiffness

Stiffness in the joints in the early morning period after waking is a typical characteristic of inflammatory arthritis [219]. The presence of prolonged morning stiffness is usually associated with active disease [220,221], typically improving upon movement of the joint(s) during waking hours [219]. Decreases in the duration of morning stiffness or its loss entirely

are associated with reductions in inflammation [222,223], with high sensitivity to change where disease flares are evident [190]. Several outcome measures have therefore employed a maximum time-period of morning stiffness to reflect a period of CID. However, the specific length of time chosen to reflect this disease quiescence is questionable [165], with two published definitions suggesting time periods of fewer than five [221] and 15 minutes [185] as suitable. However, quantifying the exact number of minutes of morning stiffness, or even its presence or absence in general, is challenging in certain patients with JIA. In particular, very young CYP or those with complex needs may not be able to verbalise the duration or presence of morning stiffness, and guardians may not be able to assess the duration in cases where CYP are not yet walking [157]. In addition, morning stiffness may persist, in some cases, after inflammation has been controlled where joint damage has been sustained [224] and therefore may not be suitable as the basis for pharmacological anti-rheumatic medication treatment strategies.

## Pain

One of the core symptoms of JIA is pain [134,225] but a measure of pain specifically is not included as a JIA core outcome variable. In outlining the COVs for JIA, Giannini et al suggest that the inclusion of self-reported pain in the preliminary RA core outcome set drives its inapplicability for CYP with JIA. This is cited as due to the "*measurements [being] compromised due to age-related cognitive problems*." [161]. It is unclear why, if Giannini et al considered younger people an unreliable source of pain assessment, a guardian assessment was not included instead as had been done for well-being. As a primary feature of JIA, pain can be limited to a single joint, spread to surrounding areas near to the joint or become more widespread. It can last for only a short period (acute pain), for example while a joint is inflamed but quickly resolve with effective treatment and/or can continue to persist (chronic pain), even in the absence of inflammation [225,226].

Measuring pain in CYP with a chronic disease such as JIA is challenging. Given the multifactorial nature of pain, any assessment of this symptom should include biological, psychological and psychosocial assessments. This could include a history of pain in addition to comprehensive assessment of the location, duration and experience of pain, pain-related behaviours, the impact of pain on the CYP's daily life and wellbeing and the social context within which the CYP is living [130,227]. However, no formal assessments of pain are routine in JIA, with many of the listed factors overlooked even when this important issue is raised. The most commonly used tools for measuring pain (in clinic or research) are unidimensional and include i) The Faces Pain Scale in younger CYP aged

between three and seven years old, and for older CYP and young people either a ii) visual analogue scales or a iii) numeric rating scale [226,228].

### The Child Health Questionnaire: Health-related Quality of Life

The term 'health-related quality of life' (HRQoL) has previously been used interchangeably with functional ability in JIA [229]. However, HRQoL is more than just physical impact of disease and considers the multidimensional psychological impact of disease on both wellbeing and function. This could be driven by limitations in physical and mental health in addition to the social impact of the JIA from a CYP's perspective [229,230]. To truly capture quality of life that relates to the specific disease in question, measures of HRQoL have consistently included both physical and psychosocial elements.

The Child Health Questionnaire (CHQ) [188] is one measure specifically designed to capture HRQoL in CYP. It has been developed for CYP aged five to 18 years, with completion by the CYP themselves after the age of 10. It comprises 15 subscales in two broad categories: physical health and psychosocial health [188]. Ten of the 15 subscales are used to form both the summary physical and psychosocial health score, with the other subscales excluded due to further development: physical functioning, social limitations (emotional and physical), pain and discomfort, general health perceptions, parental impact (emotional and time), self-esteem, mental health and behaviour [188,231]. The mean of items in each subscale is transformed to a 0 to 100 (100 denotes better health) scale using formula 1 below [231]:

$$\frac{Actual\ raw\ score\ (mean) - Lowest\ possible\ raw\ score}{Possible\ Raw\ Score\ Range}\ x\ 100 \qquad (1)$$

Each subscale is then standardised using Z-scores with data from the representative population. Z-scores are created using formula 2 below:

$$\frac{Subscale\ score - Population\ mean}{Population\ standard\ deviation} \qquad (2)$$

Once Z-scores have been created for each subscale, psychosocial and physical health summary subscales can be aggregated. Each Z-score is multiplied by a 'weighting coefficient', also provided for a standard population, and then summed for the preliminary physical and psychosocial scores. Weighting coefficients are different between physical and psychosocial summary scores to allow for the up-weighting of physical impact for the former and psychosocial impact for the latter summaries. These preliminary scores are then transformed to a norm based scoring system using formulas 3 and 4 below:

$$50 + (\boldsymbol{preliminary\ physical\ score} * \mathbf{10}) \tag{3}$$

$$50 + (\boldsymbol{preliminary\ psychosocial\ score} * \mathbf{10}) \tag{4}$$

Means and standard deviations from the representative sample can then be used to ascertain how physical or psychosocial scores of a study sample, say of CYP with JIA, compare to the general population [231]. For example, it is common to use a cut-off using this standardised scale of two standard deviations below the population mean to denote poorer versus better psychosocial health [188,231].

The CHQ has good classification validity, with ability to discriminate between healthy CYP and those with JIA; CYP with JIA score substantially lower than healthy CYP, particularly those within the systemic, polyarticular and extended oligoarticular onset categories across the 15 CHQ domains [188]. In addition, within JIA, CHQ scores across the majority of domains were able to discriminate between CYP with differing levels of functional ability [188]. However, the scoring system is complex and would likely need embedding into an electronic clinical record, further time or personnel to calculate the score for each CYP.

### 2.3.4.3 Summary: Single Outcome Measures in JIA

The list of COVs and other single outcome measures in JIA presented is not exhaustive but represents the main measures in regular use for CYP with JIA, either in a clinical or research setting. There are other scores and measures than have not been described, but as they are not discussed again in this thesis or used routinely with the UK NHS, they will not be discussed further.

The measures presented are useful to understand current levels of disease activity or the impact of disease on the CYP. However, individual measures of disease fail to capture the

multidimensional aspects of JIA, particularly if only a selection of measures is presented in any individual patient or within an individual research paper. Many composite scores for disease activity have therefore been developed.

### 2.3.5 Composite Measures of Disease Activity in JIA

*The Juvenile Arthritis Disease Activity Score*

*Development*

The Juvenile Arthritis Disease Activity Score (JADAS) [232], was published in 2009. The JADAS score is intended to describe current levels of disease activity at a given time point. It includes four of the COVs in JIA [156]: active joint count, physician's global assessment, parental global evaluation and ESR . These were chosen by nine paediatric rheumatologists based on existing evidence that the final two COVs, limited joint count and functional ability, were affected by disease damage rather than purely inflammation [195,232]. Other items considered for the JADAS but not incorporated included pain, deemed to be represented by the parental global assessment, swollen and tender joints, measures more common in RA, deemed to be represented by active joint count, and HRQoL, since it is influenced by factors unrelated to disease activity [195,232-234].

There are currently three JADAS scores available for use in clinical practice (Box 2). The JADAS10 includes up to 10 active joints but does not specify which joints to include.  If a greater number of joints are active, the active joint score is capped at 10. The JADAS71 includes a 71 joint count from standard JIA practice [232] (Figure 5.a) and for the JADAS27, a 27 reduced joint count is used [232,235] (Figure 5.b). ESR values under 20 are given a final score of zero. Scores exceeding 20 (truncated at 120) are transformed using the formula in Box 2 to produce a final value of between zero and 10.

*Definition*

$$JADAS10: \textit{Active joint count (using any 10 joints)} + PGA \text{ (10cm)} + PGE \text{ (10cm)} + \frac{(truncated\ ESR - 20)}{10}$$

$$JADAS27: \textit{Active joint count (using 27 joint count)} + PGA \text{ (10cm)} + PGE \text{ (10cm)} + \frac{(truncated\ ESR - 20)}{10}$$

$$JADAS71: \textit{Active joint count (using 71 joint count)} + PGA \text{ (10cm)} + PGE \text{ (10cm)} + \frac{(truncated\ ESR - 20)}{10}$$

**Box 2.** Calculating JADAS10, JADAS27 and JADAS71 scores [232]
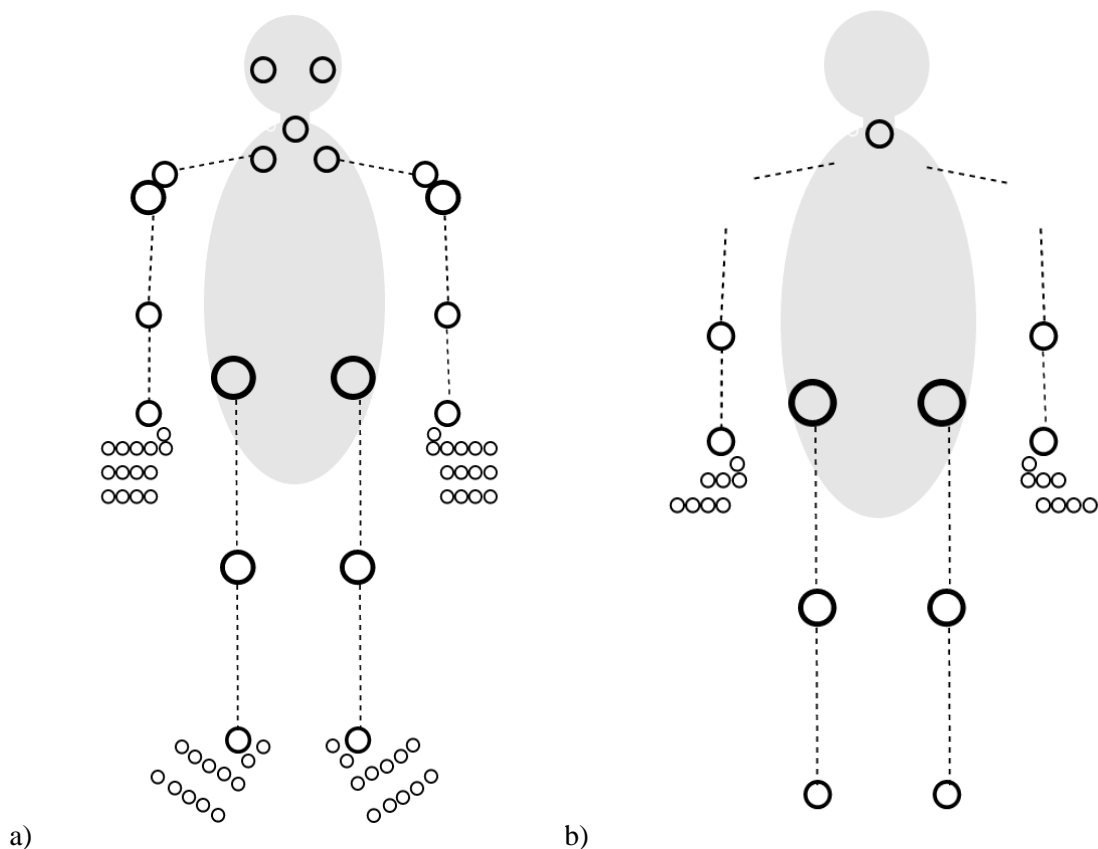
**Figure 5.** a) 71 joint count for the JADAS71/cJADAS71 b) 27 joint count for the JADAS27/ cJADAS27

*Validation*

The total highest scores possible for the JADAS10, JADAS27 and JADAS71 are 40, 57 and 101, respectively [236]. Correlation of the scores with other outcomes in JIA were largely similar across the three JADAS options, at between r=0.5 and r=0.51 against CHAQ scores to r=0.76 to r=0.78 against restricted joint count [232]. In addition, all scores could discriminate between patients who had experienced different levels of response from a trial of meloxicam and naproxen and a trial of MTX. Finally, strong responsiveness to clinical change was demonstrated [232].

*The Clinical Juvenile Arthritis Disease Activity Score*

*Development*

One of the challenges in applying the JADAS in route clinical practice is that many CYP do not routinely have blood taken to measure ESR [198]. To overcome the limitations with including ESR in the JADAS tools, a modified clinical JADAS (cJADAS), which excluded ESR, was developed [198] and further validated [186]. The cJADAS also has three versions using the 10, 27 and 71 joint counts (Figure 5; Box 3).

*Definition*

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**cJADAS10: Active joint count (using any 10 joints) + PGA (10cm) + PGE (10cm)**

**cJADAS27: Active joint count (using a 27 reduced joint count) + PGA (10cm) + PGE (10cm)**

**cJADAS71: Active joint count (using a 71 joint count) + PGA (10cm) + PGE (10cm)**

---

**Box 3.** Calculating cJADAS10, cJADAS27 and cJADAS71 [198].

*Validation*

Scores on these three measures total 30, 47 and 91, respectively [236]. The cJADAS demonstrated excellent correlation with the original JADAS, with correlation coefficients exceeding 0.9 across all  ILAR categories [198]. In addition, moderate to high concurrent validity was demonstrated for the cJADAS score against other assessments of disease activity ($r=0.5$ against limited joint counts and pain to $r=0.8$ against active joint count). However, poor concurrent validity was demonstrated against ESR ($r=0.3$).[198] In terms of feasibility, in a prospective inception cohort of 956 CYP, the full JADAS could be calculated in 37%, compared with 58% on the cJADAS at initial presentation to paediatric rheumatology [198].

### Interpreting the JADAS or cJADAS score

It is not clear currently how often the JADAS or cJADAS scores are being used in clinical practice and in part this is related to the fact that until recently it has not been possible to interpret the score in relation to what entails high or low disease activity. The score is also not linked to any specific treatment pathway or treatment decisions.  The next section of this thesis considers composite definitions of disease state, including CID and remission as well as minimal disease states. Where JADAS or cJADAS score cut-offs have been proposed, these will also be discussed.

## 2.4 Composite Measures for Assessing Disease State in JIA including Remission, Clinically Inactive Disease and Minimal Disease Activity

Measuring remission in JIA is effectively an extension of measuring disease activity, since remission, by definition, is the absence of disease activity. A single instance of this state, in JIA, has been termed CID. After achieving CID, disease activity may flare or CID may persist. Persisting CID over a length of time defines remission. If a CYP remains on anti-rheumatic therapy, this is then classed 'remission on medication' (CRM), with maintaining CID without the use of pharmaceuticals, 'remission off medication' (CR), the current optimal outcome in JIA [237].

In a heterogeneous disease such as JIA, ruling out absolutely all signs and symptoms of the disease would require a huge wealth of data including many biological and imaging tests plus patient-reported measures to assess the psychosocial impact of active disease [165]. Currently, such tests either do not exist or are not feasible to implement in every patient. Therefore, determining states of CID and remission are currently based on assessments of the COVs and/or using composite outcomes as surrogates for the absence of disease.

Due to the heterogeneity of the signs and symptoms of JIA and the lack of a gold standard test for remission and its associated states, multiple criteria sets have been developed and validated [165,168,185-187].

### 2.4.1 Clinically Inactive Disease

#### 2.4.1.1 Wallace's Preliminary Criteria for Clinically Inactive Disease, 2004

*Development*

The first composite score for CID, Wallace's preliminary criteria, was created as the use of biologic therapies became more widespread for JIA and remission-like states became more common for patients with this condition. The authors identified that recently published papers had rarely used the same outcome definitions, and therefore aimed to create a tool that could be used in a standardised manner across paediatric rheumatology clinics; this tool therefore needed to include components that were feasible to collect in routine clinical practice [165].

The initial long-list of components to include in the CID criteria set was developed using a Delphi process. Paediatric rheumatologists who were members of five rheumatology societies and organisations were asked to suggest variables for inclusion in a composite measure of CID. Components that were suggested by over 80% of participants were

carried forward straight into the definition for CID. Those suggested in between 10% and 80% were carried forward for further discussion at a consensus conference attended by 20 senior paediatric rheumatologists. The definition that was decided upon by the end of the conference included five physician-assessed components. However, these were designed for patients with select categories of JIA, with the authors noting that several disease features of the rarer categories were not taken into account [165] (Box 4, Table 3).

*Definition*

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**CID: No active joints, no systemic features, no active uveitis, normal ESR or CRP (if both tested, both must be normal) and a score of 0cm on the physician's global assessment of disease activity.**

---

**Box 4.** The definition of CID according to Wallace's preliminary criteria [165].

*Validation*

The validation process for CID according to Wallace's preliminary criteria was performed according to the OMERACT filter. For the truth domain, face and content validity were tested in an audience of approximately 250 paediatric rheumatologists across 34 countries. The authors state that i) the consensus conference and ii) the suggestion that elements of other published criteria for CID were included in the final set, as evidence of face and content validity [181]. It is unknown how acceptable these criteria are to patients. Construct and criterion validities were not tested for the CID definition.

For the discrimination filter, classification validity was not tested for CID versus active disease. Responsiveness of the measure was tested to see if CYP could shift from CID to active disease within a time course. This was tested in the same three clinics as previously described [238] and demonstrated that CYP could experience multiple episodes of each disease state. Whilst the authors attributed these results as evidence of responsiveness to the natural history of JIA [181], they did not test other parameters of disease to ascertain if the 'flares' corresponded with worsening in other signs and symptoms of the disease. Thus, responsiveness to change was not demonstrated. Finally, reliability was assessed for a proportion, but not all, of the components of the criteria set, but clinicians did not independently apply the whole set to the same CYP [181]. Therefore, the reliability filter for the criteria set as a whole was not met.

The final OMERACT filter is feasibility [180]. The authors state that during the Delphi process, the participants were mindful to create a criteria set that fulfilled the feasibility filter. However, since clinicians (and no other parties) assessed the full set outside of this

consensus meeting, it is unclear if the feasibility validation filter has been met [181]. For one component, ESR, further work has shown that this measure is not feasible to use in every CYP, since ESR is not routinely collected in all patients with JIA [198].

### Strengths and Limitations

As the first composite set of criteria for CID in JIA, Wallace's preliminary criteria identified the first partially-validated state to use as a potential treatment target. The Delphi process was far-reaching in terms of variety of paediatric rheumatology professionals across the globe and an attempt was made to validate the criteria both internally and externally across OMERACT filters [181]. However, many of the validation filters were not met. The altering of the criteria for validation purposes precludes the original definition from validation. Finally, at no point in the development or validation process were patients and/or their guardians consulted.

### 2.4.1.2 ACR Provisional Criteria for Clinically Inactive Disease, 2011

### Development

Several years after the publication of Wallace's preliminary criteria [165], an update to the criteria was provided: the ACR provisional criteria. The reason for the update of the criteria is unclear, only that a phase III trial of infliximab [239] "*indicated that changes be made…to maximize validity*" [185].

To develop these new updated criteria, 60 patient visits (out of 1096) from the infliximab trial [239] were extracted for the study; all had low or no disease activity. The authors do not discuss the implications of not including CYP with moderate or high disease activity in this exercise. However, these patients would have undoubtedly been useful in assessing discriminant validity of the new criteria set. Forty paediatric rheumatologists rated the low or inactive disease visits as being in CID or active disease using both physician and patient-reported variables from the trial: active joint counts, limited joint counts, duration of morning stiffness, physician's global, parental global, functional ability, pain and four laboratory assessments: ESR, platelets, haematocrit and white blood cells [185]. A forward stepwise logistic regression model was then used to select the set of variables that were independently ($p<0.05$) associated with the physician's 'gold standard' rating of CID. The new model was then tested against the physician likelihood rating via receiver operating characteristics. A final modification was then made after assessing face and content validity of the model with the physicians previously involved in the development of this and/or Wallace's preliminary criteria (Box 5, Table 3) [185].

*Definition*

> **CID: No active joints, systemic features or uveitis, normal ESR or CRP (if elevated, not attributable to JIA), zero on the physician's global assessment and morning stiffness ≤15 minutes.**

**Box 5**. Definition of CID according to the ACR provisional criteria [185].

*Validation*

Face and content validity of the final ACR provisional criteria were tested according to the judgement of 60 paediatric rheumatologists, all of whom had been involved in the process of creating the new 2011 criteria (n=40) or Wallace's preliminary criteria (n=20) [185]. Whilst this filter may have been met, external judgement from both healthcare professionals who were not involved in the process in addition to the patients themselves may have strengthened this assessment. Criterion and classification validities were tested via sensitivity, specificity and receiver operating characteristic values of area under the curve compared with 'gold standard' physician likelihood ratings. Whilst specificity against the physician's original judgement was 100%, sensitivity was only 33%. Thus, in a CYP with clinically inactive disease, this criteria set performs worse than chance at identifying them in a physician-assessed state of CID. The criteria were then altered to include changes to the definition of uveitis, normal ESR and morning stiffness but this test was not re-examined. Therefore, the intermediate criteria had high classification validity, but poor criterion validity. Since the analyses for testing criterion and classification validity do not appear to have been repeated in the updated criteria set, they are unclear for the final ACR provisional criteria. Feasibility, inter and intra-rater reliability were not tested for the these provisional criteria [185].

*Strengths and limitations*

The ACR provisional criteria [185] provided an update to Wallace's preliminary criteria [165], which clarified elements that were unclear in the previous set, such as 'no uveitis' and 'normal ESR'. However, the addition of morning stiffness appears to have been a statistical, rather than clinical judgement. This has compromised the feasibility of implementing this outcome measure in clinical practice, with morning stiffness not easily collectible in all patients, particularly those of young age [157]. As with Wallace's preliminary criteria, patients and/or guardians were not included in the development or validation process. Only physicians have judged these states and formed the bases of these criteria. There are additional issues with using purely physician judgement in the

development of this criteria set. Physician judgement was used as 'gold standard' for CID. However, models were based on those same physician judgements. It stands to reason that a model based on physician judgement will show good agreement with the original judgement. Thus, whilst criterion and classification validities have been reported for the intermediate criteria set, these should be taken with caution. External physician judgement would have been preferable, however this is also not a 'gold standard', nor even a desirable option as a comparator, given the variation and unreliability of 'expert opinion' in the hierarchy of evidence [166]. To have developed the optimal 'gold standard' based on available evidence would have entailed estimating a set of criteria that resembles a state of absent disease activity and predicts optimal outcome in JIA from available, published literature.

## *2.4.1.3 Defining Clinically Inactive Disease using the JADAS, 2012*

### *Development*

In response to the lack of patient/parent measure in Wallace's preliminary criteria [165], a cut-off of the JADAS was proposed as an alternative definition of CID, since the JADAS incorporates both physician and patient/parent assessments [240]. This cut-off was selected based on a comparison with CID on Wallace's preliminary criteria using a threshold of 90% specificity under receiver operating characteristic analyses [165,168] and on whether the CYP had oligoarticular or polyarticular course JIA (Box 6, Table 3). The definitions of oligoarthritis and polyarthritis used were not defined using ILAR classification [1]. Instead, patients with persistent oligoarthritis fell into the former category and those with systemic, RF-negative or RF-positive polyarthritis were deemed 'polyarthritis'. CYP in the remaining ILAR categories were classified according to whether they had fewer than (oligoarthritis group) or greater or equal to (polyarthritis group) five joints affected during their course of disease.

Defining cut-offs through comparison with existing criteria sets meant that JADAS cut-offs were based on published evidence rather than consensus through Delphi. Although this may represent a preliminary stage of criterion validity, to truly validate the cut-off in this domain would have required testing in an external dataset. However, no external validation was performed against this definition [240].

*Definition*

CID: Total JADAS score ≤1 for both oligoarticular and polyarticular course JIA.

**Box 6.** Classifying CID according to the JADAS

*Validation*

Both internal and external validation for construct validity and external validation for classification (discriminant) validity for CID cut-offs on JADAS scores were performed.

Initially, the authors state that a sensitivity of >75% against CID on Wallace's preliminary criteria was sufficient to determine face validity. Meeting a sensitivity of >75% against this criteria set demonstrates good criterion validity. However, these cut-offs were not assessed by patients or parents and therefore their acceptability in this context are unknown.

Good construct validity of the cut-offs was demonstrated through observing increases in the proportion of patients classified as having achieved CID on the JADAS through different levels of response to infliximab in the development dataset [168]. In an external, cross-sectional population of CYP with JIA for at least five years at two Italian clinics [241], the proportion of CYP with CID was compared with binary measures of functional ability [200,242], joint damage [243,244] and quality of life [245]. A greater proportion of patients with good function , no joint damage and higher quality of life were demonstrated to be in JADAS CID compared with those with poor function, joint damage and poorer quality of life [168].

In a sample of patients from the investigators' clinics, good classification validity of the cut-offs was suggested in that a greater proportion of CYP who achieved CHAQ [188] scores of zero at their last follow-up (78% CHAQ=0), or CID according to Wallace's preliminary criteria [165] (42% in Wallace CID), had JADAS CID at their initial visit compared with CYP who had not been in JADAS CID (54% CHAQ=0, 28% Wallace CID) [168]. In addition, in a population of 177 patients with polyarticular JIA with radiographic imaging data [246], CID on the cJADAS during follow-up was associated with lesser radiographic damage at three years (median cJADAS 1.3 for initial CID versus 7.8 for no CID) [168]. Neither inter or intra-rater reliability, nor feasibility analyses, were tested for the cut-offs. Therefore, partial validation of the scores has been completed.

*Strengths and Limitations*

Since the original JADAS tool does not contain components measuring extra-articular features such as enthesitis, psoriasis or systemic features, these features may persist in

CYP classified in CID. However, the inclusion of the physician and parent global assessments within the JADAS tool may, at least partially, take these features into account. In accordance, the inclusion of both physician and patient/parent-reported outcomes allows the cut-offs to define a disease state that may be relevant to both parties in the clinic. Although the types of validation were limited, good classification validity was observed not just for a single time point, but in longer-term longitudinal studies of multiple outcomes. The JADAS cut-points therefore identify clinically-relevant disease states in terms of patient outcomes. However, the limitations in feasibility of this instrument prompted the development of cJADAS cut-points [186].

### 2.4.1.4 cJADAS Cut-offs for Clinically Inactive Disease, 2014

#### Development

The same dataset of patients in which the JADAS cut-offs had been developed was used to develop those on the cJADAS. Patients were classified into oligoarticular and polyarticular course JIA as per the JADAS cut-offs tool. However, for unclear reasons, patients with systemic JIA with active systemic features were excluded from this analysis [186].

Conversely to the JADAS cut-off, that on the cJADAS for CID was gained through comparisons with CID according to the ACR provisional criteria (Box 7, Table 3) [185,186].

#### Definition

> **CID: Total cJADAS score ≤1 for both oligoarticular and polyarticular course JIA.**

**Box 7**. Classifying CID according to the cJADAS

#### Validation

The authors state that face validity of the cut-offs was gained through ensuring that a minimum sensitivity of 75% was evident compared with the proxy development measures. However, like the JADAS cut-off, demonstrating a sensitivity of >75% suggests good criterion validity.

Further validity was tested in two samples of patients from the authors' clinics. These two samples comprised a longitudinal inception cohort of patients observed for two years [247], the second a cross-sectional study of patients with at least five years of disease duration [241]. Construct validity was tested with measures used in routine clinical practice: physician and parent global assessments, parents' satisfaction with their CYP's current disease and pain in the first sample of incident cases. For all of these measures, better outcomes were progressively experienced across high disease to CID. For example, the percentage of

parents satisfied with their CYP's disease outcome increased from 27% from those with high disease activity to 95% of those in CID. Similarly, the median pain and parental global evaluation scores were both median 5cm for high disease activity (IQR pain 3, 7; IQR parent global 5, 7) and 0cm for those in CID (IQR pain 0, 0; IQR parent global 0, 1).

In the second sample of prevalent cases, classification validity was tested against poor versus good functional ability [200,242,248] and the absence versus presence of joint damage [244,249]. Good classification validity was demonstrated with ten times the odds of CHAQ≠0 in high disease activity (95% CI 5, 22) compared with CID and six times the odds of a non-zero score on the Juvenile Arthritis Damage Index focusing on articular features (JADI-A) (95% CI 2.8, 13). However, no significant differences in CHAQ scores (p=0.48) and JADI-A scores (p=0.31) were observed between patients having fulfilled CID versus low disease activity cut-offs.   Feasibility, inter and intra-rater reliability were not tested for these cut-offs.

### *Strengths and Limitations*

Although feasibility testing has not been completed for the cJADAS cut-offs, all elements of the cJADAS are easily acquired in routine clinical practice. However, like the JADAS, specific cut-offs or additional factors were not added for patients with systemic, enthesitis-related or psoriatic JIA, in addition to those that may experience uveitis. The cut-offs developed for CID underwent several different external validation procedures and were reported to have good construct and classification validity. No patients or physician external to the study were reported to have been consulted on this topic. It is therefore unclear if the measure is acceptable to these groups.

### 2.4.2   Definitions of Remission

#### *2.4.2.1 Wallace's Preliminary Criteria for Remission on and off Medication, 2004*

### *Development*

In addition to developing a definition for the state of CID, Wallace et al. also developed definitions for remission on medication and remission off medication using similar processes as previously described. The latter two states are mutually exclusive. However, both remission on and off medications involves first achieving CID, with time and medication requirements for remission on and off medication [165] (Box 8).

*Definition*

> **Remission on medication: Clinically inactive disease maintained for six months on medication.**
>
> **Remission off medication: Clinically inactive disease maintained for 12 months whilst off medication.**

**Box 8.** The definitions of remission on medication and remission off medication according to Wallace's preliminary criteria

*Validation*

The validation process for remission off medication was more comprehensive than that for CID or remission on medication. As mentioned previously, face and content validities were assumed given consensus agreement by paediatric rheumatologists on the items to include in the criteria sets and that certain components were included in other definitions for CID/remission. It is unknown how acceptable these criteria sets are to patients/guardians.

To test construct validity, agreement was tested with two definitions of remission off medication in the authors' cohort comprising a single retrospective cohort of three clinics; Two of these clinics were in the US and a third in Italy [238]. Remission on medication was not tested [181]. Although agreement was high between the two pairs of measures, as described below, it is unclear if the full criteria for remission off medication were applied to this cohort. Therefore, construct validity cannot be inferred for any of the Wallace's preliminary criteria states.

Criterion validity had to be tested through concurrent validity. Concurrent validity was tested through assessing the proportion of CYP identified by two published external definitions of remission off medication in the literature in two external populations [250,251] as well as the authors' retrospective Italian and US population [238]. One definition was broad, describing a state of 'absence of arthritis'. The other was marginally more detailed, with inclusion of specific 'active joint' and 'laboratory test' terms [250,251]. However, neither gave specific components or meaning of 'active arthritis', in order for their definitions to be reproducible. This is evident in the authors' own statement that construct validity can be tested "*If one assumes that no active arthritis means inactive disease by our criteria*". For the validation, the authors altered the definition of remission off medication according to Wallace's preliminary criteria for greater similarity to the original authors' definitions. Even with these changes, there was a significant difference with no overlap in 95%

confidence intervals between CYP identified in remission off medication in the first population studied by Oen et al. [251], and a borderline significant difference in the second population studied by Fantini et al, with confidence intervals that only marginally overlapped [250]. Although similar estimates of remission off medication were attained when all definitions of remission off medication were applied to the author's cohort [181], it is unclear whether original or altered definitions of Wallace's preliminary criteria were being applied. Thus, for remission off medication, external criterion validity has not been met and internal validity is unclear from the results presented. In addition, criterion validity was not considered for remission on medication.

Classification validities of the two remission definitions compared with CID were explored. The difference in flare rate between CYP who had achieved versus not achieved CID was tested in the author's retrospective Italian and US population [238]. The filter for classification was met in this population: time to flare was longer in remission on medication (median 14 months; IQR 9, 21) compared with CID (median 5 months; IQR 3, 6) and the longest in remission off medication (median 29 months, IQR 17, 45) [181]. Responsiveness and reliability of the remission definitions were not assessed. Finally, feasibility of implementing the remission definitions was not assessed beyond that discussed for CID.

### *Strengths and Limitations*

Many of the strengths and limitations for CID according to Wallace's preliminary criteria apply to the definitions for remission on and off medication. Further validation steps were taken for remission off medication compared with CID or remission on medication. However, it is not apparent why the remission on and off medication criteria were defined separately and were deemed mutually exclusive. Since there were (and still are) no formal guidelines on the tapering of therapies in JIA, external validation of these definitions in the same population may have eluded to an issue with these definitions regarding tapering that will be discussed in a later section.

### *2.4.2.2 Comparison of Scores for Clinically Inactive Disease and Remission*

The multiple definitions of CID in JIA have not been directly compared with each other in an external dataset to understand who they capture in regards to fulfilling the CID criteria. This is important to consider, especially if one of more of the states are selected as treatment targets in either clinical trials or clinical practice. The differences in components suggest that different disease constructs may be captured across the definitions. Wallace's

preliminary criteria and the ACR provisional criteria include measures of articular and extra-articular inflammation. In contrast, the JADAS and cJADAS capture articular inflammation, albeit over fewer measures, in addition to patient wellbeing. Therefore, in theory, a CYP could be classified as having CID according to the Wallace or ACR criteria but have ongoing pain and/or functional limitations. This is less possible using the JADAS score, but a child who achieves JADAS CID may have ongoing uveitis or systemic features which may not necessarily be captured in the physician or patient scores. Also, no validated definition of CID/remission currently includes enthesitis or psoriatic features of JIA as distinct components.

Further differences between the proposed definitions for CID/remission are the requirement to fulfil all criteria on Wallace's preliminary criteria and the ACR provisional criteria but score below a certain cut-point on the JADAS/cJADAS. Since the cut-off for CID on these latter measures is one, it remains to be seen whether CYP with one active joint may be misclassified as having CID if all other measures were zero. It could be argued that it would be unlikely for both a parent and physician to score zero on a VAS where there is evidence of joint activity. However, misclassification may occur in the opposite direction where physicians are hesitant to mark zero on their PGA, instead marking marginally higher at 0.1 or 0.2cm. These CYP would not be classified as CID using either Wallace's preliminary criteria or the ACR provisional criteria but would be using the JADAS. Further study of these outcomes within the same cohort may provide insight on these potential limitations.

**Table 3.** Comparison of definitions for CID for JIA

| Definition | Components | | | | | | | How to score CID |
|---|---|---|---|---|---|---|---|---|
| | **Active joint count** | **Physician's global assessment** | **Patient/parent global assessment** | **ESR** | **Systemic features** | **Uveitis** | **Morning stiffness** | |
| Wallace's preliminary criteria [165] | ✓ | ✓ | | ✓ | ✓ | ✓ | | Zero active joints, systemic features and uveitis, a score of zero on the PGA and normal ESR and CRP (undefined) |
| ACR provisional criteria [185] | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | Zero active joints, systemic features and uveitis, a score of zero on the PGA, normal ESR and CRP and morning stiffness ≤15 minutes |
| JADAS (10, 27, 71) [168] | ✓ | ✓ | ✓ | ✓ | | | | Total score≤1 |
| cJADAS (10, 27, 71) [186] | ✓ | ✓ | ✓ | | | | | Total score≤1 |

CID: Clinically inactive disease, ACR: American College of Rheumatology, JADAS: Juvenile Arthritis Disease Activity Score, cJADAS: clinical JADAS, PGA: Physician's global assessment, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

### 2.4.3 Minimal Disease Activity

Unfortunately, within the limits of current therapies for JIA, some CYP may never reach remission or even CID at a single time point. In these cases, continuing to aggressively escalate treatment may not appreciably improve disease activity, pain or wellbeing further. These treatment strategies may confer an added risk of increasing toxicity of treatment, with little benefit. Intermediate disease states have therefore been proposed as an alternative treatment target, such as minimal disease activity (MDA) [168,187]. The first definition of MDA was developed by Magni-Manzoni et al. in 2008 [252].

### 2.4.3.1 Magni-Manzoni Definition of Minimal Disease Activity, 2008

*Development*

Magni-Manzoni et al.'s definition of MDA was the first to be proposed and validated for CYP with JIA. Their definition was originally proposed as a treatment target for CYP with polyarticular JIA, the majority of whom had not achieved remission in published clinical trials [187].

To develop a new measure of MDA in JIA, a consensus between study investigators combined with a literature review classified CYP into what they considered a state of high or minimal disease activity. The CYP were selected from a retrospective cohort of 414 patients with at least one clinic visit between 1988 and 2003 [187]. In this initial stage, the decision on whether a CYP had high or minimal disease was based purely on medication strategies. For example, a criterion for high disease activity was new, restart or increased dose of prednisolone, and MDA not changing a second-line therapy or biologic for at least one year. Following these classifications, all measures of disease activity (both inflammatory and non-inflammatory) captured in these CYP were considered for inclusion to the criteria. This was completed in all ILAR categories except enthesitis-related JIA, due to both the differential disease features and low numbers in this subgroup.

Cut-offs on the variables considered for the MDA definitions were selected through highest area under the curve analyses using receiver operating characteristics. For these analyses, patients were divided and analysed separately if following one of two courses based on the number of affected joints: i) oligoarticular JIA, to include patients with persistent oligoarthritis and  ii) polyarticular JIA, to include patients with extended oligoarthritis, polyarthritis and systemic arthritis. Patients with psoriatic or undifferentiated arthritis were classified based on the number of active joints they experienced through their disease course. It is unclear whether this relates to the total highest overall or at a

single time point. Finally, the preliminary set of MDA criteria for each category was defined in separate multivariable logistic regression models using backwards stepwise selection methods. The model with the highest predictive ability was then partially validated (Box 9, Table 4) [187].

*Definition*

> **Oligoarthritis course: no active joints and physician's global score ≤2.5cm.**
>
> **Polyarthritis course: no active joints, physician's global score≤3.4cm and parental global score≤2.1cm.**

**Box 9.** Definitions for minimal disease activity according to Magni-Manzoni et al [187].

*Validation*

The authors attempted to attribute a lack of patients with minimal disease activity at baseline in trials as evidence of face validity, however this is not without its limitations. Patients enrolled in clinical trials may be more likely to have severe disease. This test of face validity therefore does not distinguish between minimal and moderate disease states not observed frequently in these cohorts at this initial time point. Content validity was not tested. Construct validity was assessed through associating minimal versus high disease activity against non-inflammatory measures of the impact of JIA, including functional ability [248], quality of life [248] and radiographic damage [249]. For oligoarthritis, good construct validity was demonstrated across two of three measures of function (Median $CHAQ_{MDA}=0$ (IQR 0, 0), $CHAQ_{No\ MDA}=0$ (IQR 0, 0.25); Median $LJC_{MDA}=0$ (IQR 0, 0), $LJC_{No\ MDA}=1$ (IQR 0, 1); Median Steinbrocker class II-III$_{MDA}$= 2.6%, Steinbrocker class II-III$_{No\ MDA}$= 13.4%) but not damage (Median $JADI_{MDA}=0$ (IQR 0, 0), $JADI_{No\ MDA}=0$ (IQR 0, 0)) or quality of life (Median CHQ psychosocial$_{MDA}$: 47 (IQR 44, 54), CHQ psychosocial$_{No\ MDA}$= 52 (IQE44, 57)). In polyarthritis, greater construct validity was evident with statistically significant differences in all measures tested between MDA and high disease. However, absolute differences were small, challenging the clinical significance of these findings [187]. Criterion validity was not tested.

For discrimination, classification validity was tested against two measures of improvement: ACR Pedi responses [161], which assess the proportional change across the range of the 6 JIA COVs, and a physician judgement of improvement. Overall, there were significant differences in the proportions of patients classified in minimal disease activity across four ACR Pedi categories and through 'improved' versus 'not improved' clinician

judgement. However, as a measure of a static disease state, classification validity would have been better demonstrated against other static disease states in addition to variables of change, such as Wallace's preliminary criteria for CID, which had been published four years previously [165]. It is unknown whether this measure was available at the start of the process for developing the definition for MDA. Responsiveness, reliability and feasibility were not assessed.

### *Strengths and Limitations*

Strengths of this measure include it being the first developed criteria for MDA and partial validation in nearly all JIA categories [187]. In addition, a large selection of potential variables to form the score was considered, comprising both inflammatory and non-inflammatory measures. These measures were taken from data already present in a routinely-collected clinical dataset. Potential components of the score therefore had to be feasible to collect in some part before entry into the selection procedure, increasing the clinical applicability of the final measure [187]. However, data for the study were retrospective and therefore susceptible to selection bias. CYP in the study may have had poorer disease activity than a prospective cohort given the observation that CYP lost-to-follow-up in clinical studies often have better disease activity [250]. Given a wide range of high disease activity in retrospective data, cut-offs for low activity may therefore have been less stringent given these data, compared with prospective data with a greater range of CYP with low disease activity. This issue might have been mitigated through external validation in a prospective dataset, which was not performed. In addition, face and content validity of the minimal disease criteria were likely limited. The initial proxy definitions of minimal and high disease activity were based purely on changes or persistence using medications, not taking patient opinion of low and high disease activity into account [187]. This is also a likely factor in explaining the low construct validity across some of these analyses, particular in oligoarticular course JIA. However, the final measure includes both physician and patient-reported outcomes for polyarticular course JIA [187].

### *2.4.3.2 Minimal Disease Activity Defined using JADAS Cut-offs, 2012*

### *Development and Validation*

The MDA state previously discussed by Magni-Manzoni et al. does not include any patient/parent assessments for oligoarthritis [187]. Therefore, similar to the development following Wallace's preliminary criteria for CID, MDA cut-offs on the JADAS were proposed in order to define disease activity states relevant to both patients and clinicians.

Similar to the original definitions of MDA proposed by Magni-Manzoni et al. [187], cut-off values on JADAS tools were defined according to whether the CYP had an oligoarticular or polyarticular course JIA. An optimal cut off for MDA was determined based on highest area under the curve estimates using receiver operating characteristics against the Magni-Manzoni minimal disease definition. A cut-off score was proposed for all three calculations of the JADAS score (10, 27 and 71 joints) (Box 10, Table 4) [168,187].

Validation, strengths and limitations of cut-offs on the JADAS for disease activity states have been previously discussed. However, criterion and classification validity of the cut-offs were not tested against the Magni-Manzoni MDA definition in an external population at a static time point.

### *Definition*

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**Oligoarthritis course: Total score ≤2 (cut-off similar on all three JADAS measures).**

**Polyarthritis course: Total score ≤3.8 (cut-off similar on all three JADAS measures).**

---

**Box 10.** Defining minimal disease activity on the JADAS

### *2.4.3.3 Minimal Disease Activity defined using cJADAS Cut-offs, 2014*

### *Development and Validation*

The development, validation, strengths and limitations for disease activity states using the cJADAS have been previously discussed. Additionally, cut-offs on the cJADAS tools for MDA were assigned, as determined through receiver operating characteristic analyses (Box 11)[187]. Criterion and classification validity of the cut-offs were not tested against the original Magni-Manzoni or previous JADAS MDA cut-offs in an external population at a static time point [168,186].

### *Definition*

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**Oligoarthritis course: Total score ≤1.5**

**Polyarthritis course: Total score ≤2.5**

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**Box 11.** Defining minimal disease activity on the cJADAS

### *2.4.3.4 Comparison of Scores for Minimal Disease Activity*

Despite the lack of direct validation between the JADAS/cJADAS [168,186] MDA cut-offs and the Magni-Manzoni definition [187], there is likely high concordance between the three MDA definitions. All three include assessments of the disease and its impact on the patient by physicians and patients/guardians. In addition, all three definitions propose cut-points for MDA which differ according to the disease course experienced. However, the MDA criteria for oligoarticular course JIA in the Magni-Manzoni definition does not include any patient/guardian input. Therefore, some discordance between patients captured by this definition and those with oligoarthritis using the JADAS/cJADAS measures may be expected.

**Table 4.** Comparison of definitions for minimal disease activity in JIA

| MDA outcome | Components | | | | Scoring for MDA |
|---|---|---|---|---|---|
| | AJC | PGA | PGE | ESR | |
| Magni-Manzoni [187] | | | | | Persistent oligoarticular:<br>- Active joint count=0<br>- Physician's global≤2.5cm |
| | ✓ | ✓ | ✓ | | Extended oligoarticular, polyarticular, systemic:<br>- Active joint count≤1,<br>- Physician global≤3.4cm<br>- Patient/parent global≤2.1cm |
| JADAS (10, 27, 71) [168] | ✓ | ✓ | ✓ | ✓ | Oligoarticular course≤2.0<br><br>Polyarticular course≤3.8 |
| cJADAS (10, 27, 71) [186] | ✓ | ✓ | ✓ | | Oligoarticular course≤1.5<br><br>Polyarticular course≤2.5 |

JIA: Juvenile idiopathic arthritis, MDA: Minimal disease activity, AJC: Active joint count, PGA: Physician's global assessment, PGE: Parental global evaluation, ESR: Erythrocyte sedimentation rate, JADAS: Juvenile Arthritis Disease Activity Score, cJADAS: Clinical JADAS

### 2.4.4    Summary of Validation for Minimal Disease Activity, Clinically Inactive Disease and Remission Criteria Sets in JIA

The criteria sets for MDA and CID as well as remission are invaluable for potential use in standardising treatment strategies and assessment of disease activity in JIA. However, the differential development and validation methods mean that comparability is unclear. In addition, none of the criteria sets for MDA, CID or remission in JIA had any input from patients or their parents, although some of the outcomes do include a patient/parent assessment. Therefore, states of disease activity identified by the definitions described may not be meaningful to patients. These scores may aim to measure disease states encompassing a lack of inflammation and which are targetable through anti-rheumatic therapies. If so, including patient/parent reported outcomes may introduce additional disease constructs that may not fit this paradigm. However, to patients/parents, disease control may not represent a decrease in the minutes of morning stiffness from 30 to 15 minutes or the lowering of inflammatory biomarkers. Functional ability, pain and quality of life have been overlooked by the disease activity measures, despite being primary aims in the management of JIA [236]. Instead, physician opinion is used as a basis, and even a 'gold-standard' for the ACR provisional criteria [185]. The authors of this criteria set state, "*In the absence of a biologic marker for active or inactive JIA, aggregated expert judgement becomes necessary to determine criteria for clinical inactive JIA*". However, they did not incorporate published epidemiological evidence or experts in the form of patients, guardians or additional healthcare professionals. This led to a greater inclusion of physician-assessed components that may not have been based in evidence beyond anecdotal physician opinions of their assessments of patients.

Problems with expert opinion have been widely accepted in the evidence hierarchy, being outranked by all forms of published evidence in humans [166]. Before the development of further criteria for CID, evidence of long-term outcomes following achievement of certain states of disease activity needs to be ascertained. This needs to be in terms of both short and long-term outcomes and physician and parent-reported outcomes. In addition, face and content validity need assessment from not only paediatric rheumatologists, but all members of the multidisciplinary team. However, the most important party to assess these validities is the patient group themselves, who have so far not been involved in the development, validation or implementation in any of the CID/remission definitions. Without these measures, no further treatment targets should be identified for JIA.

**Table 5.** Validation information for published definitions of remission, minimal and clinically inactive disease in JIA

| Outcome definition | Year | Face | Content | Construct | Criterion | Classification | Responsive-ness | Reliability | Feasibility | Validated in which categories? | Validated in which age ranges | Any external validation | Validation in observational cohorts |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Minimal disease activity | | | | | | | | | | | | | |
| cJADAS | 2014 | ? | - | ✓ | ✓ | ✓ | - | - | - | All except symptomatic systemic | Population IQR 8.6 to 21.6 years | Yes | Yes |
| JADAS | 2012 | ? | - | ✓ | ✓ | ✓ | - | - | - | All | 0 – 22 years | Yes | Yes |
| Magni-Manzoni | 2008 | ? | - | ⊗ oligo ✓poly | - | ✓ | - | - | - | All except ERA | Unknown | No | |
| CID and remission | | | | | | | | | | | | | |
| cJADAS | 2014 | ? | - | ✓ | ✓ | ✓ | - | - | - | All except symptomatic systemic | Population IQR 8.6 to 21.6 years | Yes | Yes |
| JADAS | 2012 | ? | - | ✓ | ✓ | ✓ | - | - | - | All | 0 – 22 years | Yes | Yes |
| ACR provisional criteria | 2011 | ✓* | ✓* | - | ? | ? | - | - | - | Extended oligoarticular, polyarticular and asymptomatic systemic None with uveitis | 4 - 17 years | No | No |
| Wallace's preliminary criteria | 2004 | ✓* | ✓* | ? | ? | ✓ | ? | ? | - | Oligoarticular, polyarticular and systemic | 0.7 to >30 years. | Yes | Yes |

*According to paediatric rheumatologists and not patients/guardians. ✓= Good validity demonstrated, ?= test was not appropriate to assess validity or not tested in complete criteria set. ⊗= Tested and poor validity demonstrated, - = Not tested. JIA: Juvenile idiopathic arthritis, JADAS: clinical Juvenile Arthritis Disease Activity Score, cJADAS: clinical JADAS, CID: Clinically inactive disease, ACR: American College of Rheumatology

### 2.4.5    How often do CYP with JIA Achieve Remission?

The validated definitions for remission in JIA have only been available since 2004 [165,168,185,186]. Their uptake has not been widespread, described in a later section (See Paper 1). However, in order to assess and optimise treatment in the routine care of CYP with JIA, an understanding of how often states of MDA and CID are achieved is needed. At the time of starting this PhD (2014), no systematic reviews of how common CID or remission is achieved in JIA had been published. Such a systematic review forms the first results chapter of this thesis. Narrative reviews have estimated that between one third to two thirds of CYP achieve this disease state [253,254]. These estimates differ widely across cohorts and across studies, which have often used different outcome criteria. Despite their differences, these estimates suggest that the burden of JIA disease is high, although these reviews have largely summarised cohorts prior to the widespread use of biologic therapies. Thus, it is unclear whether the expected disease course remains this bleak in patients being treated within an era of changing treatment strategies, including biologic therapies, such as that presented in the NHS England pathway. Understanding the frequency of remission and CID in more recent cohorts is important in terms of understanding the burden of disease, for healthcare planning and to assess any impact of changes to treatments or treatment strategies.

## 2.5  Predictors of Remission

There may be certain patient characteristics that predict, at an early stage, whether a CYP with JIA will achieve MDA, CID or remission. If predictors are known, CYP with poorer chances of achieving these states can be targeted with more aggressive early therapies, minimising the burden of unnecessary additional therapies and improving their short and long-term outcomes. Potential predictors may include characteristics ranging from demographic features, such as age and gender, to more complex disease-related factors. Although environmental exposures and genetic factors may play a role in predicting these outcomes, the focus of this narrative review was on demographic and clinical factors.

### 2.5.1    Considerations Regarding Outcome Definitions across Studies
### Assessing Predictors of CID/remission

A total of 32 studies were identified which assessed predictors of CID or remission for patients with JIA (Table 6 & Table 7). Many studies were completed before the publication of the first validated definition: Wallace's preliminary criteria [237]. However, even after their publication, many investigators continued to define their own criteria

(n=13/20). No studies focusing of predictors of these disease states have, to date, used the JADAS or cJADAS cut-offs as outcomes.

For investigators defining CID/remission *not* according to Wallace's preliminary criteria (n=25), 13 specified the absence of medication within their criteria sets. Thus, certain investigators considered remission to only have been achieved in the absence of anti-rheumatic drugs. Having no signs of disease in the presence of these therapies is likely a different disease construct to having no sign in the absence of therapies. One defines a state where disease activity may continue to be propagated, but is controlled by pharmaceuticals. The other defines a state where, without control through medication, the inflammatory disease processes, even if present, are not severe enough to produce observable clinical signs of disease. Thus, different predictors for achieving these disease states may be expected.

In addition to differences in requirements for medications, 12 investigators created or used non-validated definitions of remission that included the maintenance of CID for some period of time. This ranged from 'under two years' [255-258], with the lowest objective period of time specified at three months [259,260] to at least two years [255-258,261,262]. Here, the investigators did not consider a short transient phase of CID to constitute 'remission'. Since JIA is a disease of remission and relapse [7], different predictors of short periods versus longer periods of maintaining CID may be expected.

There were also differences in the definitions regarding the inclusion or exclusion of patient-reported variables. Of the 34 studies, only six included any patient-reported factors: the patient/parent global assessment of wellbeing (n=1) [263], pain (n=4) [261,263-265], fatigue (n=2) [264,265], functional ability (n=1) [259] and a broad statement regarding 'no symptoms' (n=1) [260]. Thus, the vast majority of studies assessing predictors for CID/remission in JIA are assessing predictors of a disease state encompassing a lack of inflammation, regardless of patient wellbeing. However, the different elements of inflammation included may complicate the comparison of predictors across study populations.

**Table 6** Definitions of CID and remission in studies assessing risk factors for these states

| Study | Validated or investigator-defined definition | Definition of CID/remission | | | | | |
|---|---|---|---|---|---|---|---|
| | | Inflammatory features | Extra-articular features | Symptoms | Medication | Time | Other |
| Svantesson, 1983 [262] | Investigator-defined | No joint inflammation Normal laboratory biomarkers | - | - | No medication other than NSAIDs | At least two years | - |
| Pongpanich, 1988 [259] | Investigator-defined | 'No active disease on examination' Normal ESR | 'No active disease on examination' | Normal functional ability | No medication | At least three months | No family history (no further detail) |
| Hertzberger-ten 1992 [266] | Investigator-defined | 'Continuous' versus 'intermittent' disease | - | - | - | - | - |
| Gare, 1995 [255] | Investigator-defined | No active synovitis | No extra-articular features | - | No medication | CID: fewer than two years Remission: at least two years | - |
| Savolainen, 1998 [260] | Investigator-defined | No signs of disease Normal inflammatory biomarkers Joint limitations may be present | No signs of disease | No symptoms of disease | No medication | At least three months | - |
| Guillaume, 2000 [261] | Investigator-defined | No joint swelling ESR<15mm/hr | No uveitis | No painful stiffness | No medication | At least two years | - |
| Minden, 2000 [264] | Investigator-defined | Morning stiffness ≤15 minutes No swelling in the joints or tendon sheaths ESR<20mm/hr | - | No fatigue No joint pain No joint tenderness | - | - | Five or more of the criteria listed to fulfil |
| Al-Mater, 2002 [267] | Investigator-defined | 'Remission' yes/no | - | - | - | - | - |
| Arguedas, 2002 [256] | Investigator-defined | No active synovitis | No extra-articular features | | No medication | CID: Fewer than two years Remission: At least two years | |
| Kotaniemi, 2002 [268] | Investigator-defined | No active joints ESR<10mm/hr CRP<10mg/L | - | - | No medication | At least six months | |
| Flato, 2003 [265] | Investigator-defined | Morning stiffness ≤15 minutes No swelling in the joints or tendon sheaths ESR<20mm/hr | - | No fatigue No joint pain No joint tenderness | - | - | Five or more of the criteria listed to fulfil |
| Fantini, 2003 [250] | Investigator-defined | CID: No active joints Remission: No active joints No positive biomarkers | - | - | CID: On medication Remission: Off medication | Remission: At least six months (12 months for oligoarthritis if IA | - |

| Study | Validated or investigator-defined definition | Definition of CID/remission | | | | | |
|---|---|---|---|---|---|---|---|
| | | Inflammatory features | Extra-articular features | Symptoms | Medication | Time | Other |
| | | | | | | steroid injection) | |
| Wallace, 2005 [269] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Flato, 2006 [270] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Singh-Grewal, 2006 [271] | Investigator-defined | No active arthritis according to medical history, examination, imaging or biomarkers | No systemic features | - | - | - | - |
| Fernandes, 2007 [272] | Investigator-defined | No active joints Normal ESR/CRP | No systemic features No uveitis | - | - | - | - |
| Oen, 2009 [273] | Investigator-defined | No active joints PGA=0cm | No systemic features No uveitis | - | - | - | - |
| Albers, 2010 [274] | Investigator-defined | No active arthritis PGA=0cm Normal ESR if available | No systemic features | - | - | - | - |
| Nordal, 2011 [275] | Wallace's preliminary criteria as assessed by treating physician. Corrected by investigator if disease parameters inconsistent | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Berntson, 2013 [276] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Bertilsson, 2013 [257] | Investigator-defined | No active synovitis | No extra-articular features | - | No medication | CID: Fewer than two years Remission: At least two years | - |
| Huang, 2013 [277] | Investigator-defined | No disease activity | No disease activity | - | No medication | - | - |
| Russo, 2013 [278] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Albers, 2014 [279] | Investigator-defined | No active arthritis PGA=0cm | - | - | - | Time spent in CID used to determine | - |

| Study | Validated or investigator-defined definition | Definition of CID/remission | | | | | |
|---|---|---|---|---|---|---|---|
| | | Inflammatory features | Extra-articular features | Symptoms | Medication | Time | Other |
| | | ESR<20mm/hr | | | | | 'remitting' and 'intermittent' disease |
| Berntson, 2014 [280] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Guzman, 2014 [5] | Investigator-defined | No active joints PGA<1cm | No systemic features in sJIA No enthesitis in ERA or PsA No uveitis | - | - | - | - |
| Selvaag, 2014 [281] | Wallace's preliminary criteria and Investigator-defined | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | At assessments after 15 years, CID defined as no flares after 23 or 30 years, depending on time of assessment |
| Sengler, 2015 [282] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Oliveira-Ramos, 2016 [6] | Investigator-defined and Wallace's preliminary criteria | Incorporated: Swollen joint count ESR/CRP Peripheral swelling Morning stiffness Active joint count PGA=0cm | Incorporated: No systemic features No uveitis | Incorporated: Tender joint count PGE Back pain Peripheral pain | - | - | DAS28<2.6 DAS44<1.6 ASDAS<1.3 Wallace's preliminary criteria for sJIA and unclassified arthritis |
| Vilaiyuk, 2016 [258] | Investigator-defined | No active synovitis | No extra-articular features | - | Off medication | CID: fewer than two years Remission: at least two years | - |
| Alberdi-Saugstrup, 2017 [283] | Wallace's preliminary criteria | No active joints PGA=0cm Normal ESR/CRP | No systemic features No uveitis | - | CRM: On medication CR: Off medication | CRM: At least six months CR: At least one year | - |
| Glerup, 2017 [284] | Investigator-defined | No active arthritis Normal ESR/CRP | No systemic features No uveitis | - | - | - | - |

CID: Clinically inactive disease, NSAIDs: Non-steroidal anti-inflammatory drugs, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, PGA: Physician's global assessment, IA: Intra-articular, CRM: Remission on medication, CR: Remission off medication, PGE: Patient/parent global evaluation, DAS28: Disease Activity Score in 28 joints, DAS44: DAS in 44 joints, ASDAS: Ankylosing Spondylitis Disease Activity Score, sJIA: systemic JIA, ERA: Enthesitis-related JIA, PsA: Psoriatic JIA.

### 2.5.2 Predictors of Clinically Inactive Disease and Remission in JIA

*ILAR Category*

By far, the strongest predictor of remission appears to be ILAR category. Differences in prognoses between CYP with different JIA disease categories has been well documented, with patients with oligoarticular JIA appearing to achieve remission more commonly [5,256,258,264,269,273-275,277], particularly more than polyarthritis [5,255,258,259,273,275], where several studies have reported 0% achievement of these outcomes in CYP with RF-positive polyarthritis [250,258,273]. In the epidemiology of JIA, CYP with oligoarticular JIA tend to experience disease onset in early childhood with those with enthesitis-related arthritis and polyarthritis, particularly RF-positive, tending to be in late childhood or adolescence at onset [4]. They also have different gender distributions and therefore, many of the other predictors of CID or remission reported in the following sections should be considered in light of ILAR category.

*Age and Gender*

Almost every study included certain demographic factors in their analyses. Gender and age are two of the most accessible characteristics and would therefore be convenient predictors to base treatment strategies around. However, few studies have confirmed any associations between these factors with CID or remission.

Only a small number of analyses [238,255,270] have reported an association between gender and remission. In more recent cohorts when analyses were adjusted for potential confounders, gender has been consistently found to not predict CID or remission in JIA (Table 7).

Capturing age as a predictor of remission is challenging. There are multiple time points at which age might relate to prognosis: age at disease onset, age at initial presentation, age at diagnosis and age at treatment initiation. If basing treatment decisions at initial presentation on age, the former two may be the most informative. However, age at onset may be less accurately collected, as it requires recall by the patient or their guardians back to the date of first symptom(s). These differences in recall accuracy may have led to the mixed associations observed between this variable and later CID or remission. A majority of studies have not reported associations between age at JIA onset and the achievement of CID or remission at static time points or with a remitting course of disease over follow-ups that range to 15 years (Table 7).

Given the lack of association between age at onset and remission, a similar non-association might be expected between age at diagnosis and remission. However, age at diagnosis is more accurately reported than age at onset. In accordance, two studies have found associations between age at diagnosis with remission but not age at onset [272,273].

As discussed, age is also associated with ILAR category. Therefore, age at diagnosis may only be predictive in that older CYP tend to have JIA categories associated with poorer outcomes, such as RF+ polyarthritis or psoriatic arthritis. In concordance, in studies that have adjusted for ILAR category, age is only predictive of CID or remission in univariable analyses, and not the adjusted analyses [6,270,273].

### *Disease Duration*

The period of time between symptom onset and diagnosis has in itself been reported to be predictive of remission, with longer delays associated with marginally poorer outcomes [6,250,282]. This may relate to the previously mentioned 'window of opportunity', whereby there may be a finite length of time after onset of disease to most effectively treat JIA in terms of preventing poor long-term outcomes. However, these results should be taken in the context of small effect sizes where an association has been reported and in the context of either months or years of disease prior to diagnosis, with the upper bound of both confidence intervals approximating 1.0 [6,282]. In addition, a similar point estimate was gained from a large prospective inception cohort reporting a statistically significant association before, but not after, multivariable adjustment, including adjustment for ILAR category [273].

### *Sociodemographic Factors*

In a large prospective inception cohort of CYP with JIA, socioeconomic status, using the English index of multiple deprivation (IMD), has been cross-sectionally associated with poorer functional ability, wellbeing and perceptions of the impact of JIA [285]. However, the association between socioeconomic factors and remission in JIA is a largely untouched field. A single study of adults with JIA (mean age at last follow-up 34 years ± 13 years) reported no association between the number of years of education or professional activity and CID in adulthood [6]. However, this may not adequately reflect the social standing of family surrounding the CYP, and therefore their sociodemographic situation at disease onset.

*Features of JIA Disease Activity*

Factors related to the JIA-disease itself are often the fundamental basis of treatment decisions and therefore may be assumed to be the strongest predictors of the CYP's disease course. These may be factors that can be directly observed in the clinic, or those requiring further investigations using blood analyses or imaging techniques. As previously mentioned, ILAR category appears to be a strong predictor for CID and remission and it is likely that many of the associations observed with individual measures of disease activity are reflective of the underlying ILAR category, although in many studies this has not been considered.

*Active and Limited Joints*

Whilst there has been reported to be no association between limited joint count and remission [273], there is mixed evidence regarding active joint count. Few studies have associated a larger number of active joints with lower achievement of CID and remission [257,265,273]. These studies ranged from short-term CID in contemporary cohorts [273] to longer-term studies in cohorts likely with limited access to biologic therapies [257,265]. However, a more recent study in a Canadian multicentre inception cohort only reported the number of active joints predictive of CID before, but not after, multivariable adjustment. This included adjustment for ILAR category [273]. For the remaining studies finding an association between active joint counts and remission, the outcome definitions did not include the PGA, unlike several of those studies favouring no association between active joint counts and these outcomes [261,264,271,273,281]. Therefore, active joint counts may predict a low disease activity state in a pre-biologic era largely not judged to be remission by treating physicians. Whilst access to contemporary therapies may play a role in the predictive ability of joint counts and CID/remission states, there also appears to be growing evidence that location of joint activity may predict remission; Whilst the presence of knee arthritis does not predict remission [255,264,266,286], a few studies have associated hip [287] and more commonly ankle arthritis with poorer achievement of these states [255,270,286].

*Extra-articular Manifestations*

There is little evidence for extra-articular manifestations as predictors of remission. The evidence that does exist suggests that systemic features such as hepatomegaly, fever and rash predict a disease course more prone to flares within systemic JIA [271] and that enthesitis is associated with a lack of remission in ERA [287]. In addition, the presence of uveitis has been variably associated with different disease courses including a lack of remission [265,266,268,284]. However, these studies have rarely used remission definitions

which included components capturing these extra-articular features, which is vital in the continued treatment of patients experiencing these features of disease.

### Physician's Global Assessment of Disease Activity

Using current evidence, it is unclear if the PGA predicts remission. One study reported a lack of association [274], compared with two that found some association, with higher scores predicting lower achievement of remission [273,281]. However, only one of these studies assessed the predictive potential of the PGA in a multivariable model and in this case, score at 15 years was assessed as predictive of remission at 30 years [281]. It is therefore unclear if PGA scores early in the disease course predict remission.

### Parental Global Assessment of Wellbeing

In the same studies associating PGA with remission, PGE scores were also assessed as a potential predictor. Similar associations were reported between PGE score and remission, with an association only evident after multivariable adjustment between poorer wellbeing and lower achievement of remission when assessed far into the disease course of JIA [273,281]. Therefore, this association also remains unclear.

### Functional Ability

Four studies have assessed the potential association between functional ability and remission [6,257,273,281]. However, these studies suffer from the same limitations as those previously discussed. Although all four associated poorer functional ability on either the CHAQ or HAQ with lower achievement of CID or remission in univariable analyses [6,257,273,281], this association only remained evident in one multivariable analysis focusing on function in adulthood as a predictor of later remission [6]. This study was also the only one to incorporate patient-reported outcomes, PGE and pain scores, into the remission criteria. Therefore, functional ability may predict a lack of pain or good wellbeing better than a lack of inflammatory activity.

### Biomarkers

Biomarkers previously studied as predictors of remission include ESR, CRP, RF, ANA and in fewer studies, anti-collagen II and anti-citrullinated protein antibodies (ACPA), including anti-CCP. The greatest body of evidence available is for ANA, which in all studies (n=12) [6,238,256,261,265,266,271,273-275,279,284] but one [282], did not predict remission in JIA. However, this last study was a large inception cohort of multiple JIA categories, which assessed the association between ANA and remission after controlling for potential

confounders, including ILAR category. This association may have been driven by missing data bias (>40% missing for ANA). Alternatively, the specific window of time for remission, between nine and 12 months following enrolment, has not been studied elsewhere, although studies with both shorter and longer time-frames did not find this association. Therefore, although the weight of evidence is against ANA as a potential predictor of remission, the association cannot be excluded.

Like ANA, ACPA and anti-collagen II also have not been shown to predict CID or remission [6,280], although they are rarely positive in JIA and, where positive, are more frequently observed in the ILAR category with the poorest prognosis: RF-positive polyarthritis [280]. The majority of studies have also not associated RF-positivity with CID or remission [6,256,257,261,280,282], with few studies, mainly in retrospective cohorts, having associated the presence of RF with lower odds of these outcomes [265,284]. However, the retrospective nature of these cohorts may have introduced issues with selection bias. One prospective inception cohort also reported an association between RF-positivity and remission [273]. However, this analysis was univariable and therefore may be explained by a confounding factor such as age or ILAR category that was not included in the model. Given the evidence of lower remission rates in CYP with RF-positive polyarticular disease compared with the other categories, including RF-negative polyarticular JIA, it is likely that ILAR category partially or wholly explains these associations where evident.

Unlike the fixed biomarkers discussed, ESR and CRP may vary from day to day. There are almost equal numbers of publications reporting the absence of associations between either ESR or CRP and remission [261,264,266,273,281] and that elevated levels are associated with a lack of remission [267,271,281,283]. Whilst there is evidence for ESR not predicting remission in a greater number of ILAR categories [261,264,266,273,281], the evidence for CRP includes prospective inception cohorts which reported conflicting evidence; lower CRP predicted remission in the Nordic JIA cohort [283], but not CID in the Canadian ReACCh-Out cohort [273]. However, the studies had different follow-up times, used different treatments and had different remission states as outcomes, with that in the ReACCh-Out cohort not including acute phase reactants as part of the remission criteria. The associations become harder to study where dynamic biomarkers such as ESR and CRP may change over the disease course, may only be predictive at certain times in the disease course and/or where they are included in remission criteria.

### Patient-reported factors

Patient-reported factors commonly encompass complex constructs such as pain, fatigue and quality of life. These have complex drivers and may be associated with each other through various pathways [137]. However, a negligible number of studies have explored these factors as predictive of remission. The association between PGE and remission has already been discussed. In other studies, higher pain and poorer quality of life have been associated with lower achievement of CID or remission [266,273], but the majority were in univariable analyses only. Further work is needed to assess the associations between the patient-reported variables and their disease courses. These may prove vital to the prediction of remission outcomes that include patient/parent assessments of wellbeing, such as the JADAS [168].

### Previous Disease Activity

Finally, when observing a CYP further into their disease course, the strongest predictor of outcome is likely their previous outcome. CYP that have previously achieved mild disease courses or remission have been demonstrated to be more likely to achieve these states at a later stage [257,271,274,281,288,289]. In addition, the medication which the CYP has been previously prescribed may be a useful predictor of disease. For example, CYP not requiring corticosteroids [271], particularly via the systemic route of administration [274] or CYP who have required and responded to only one csDMARD [258] may have higher odds of CID and remission. Whilst response to medication may strongly predict outcome, and may be useful further into the disease course, this requires time to observe. Treatment strategies may, therefore, have to take different aspects of the CYP's disease into account as time progresses. However, a window of opportunity may exist for early in the JIA disease course where more aggressive medication may be most effective at controlling disease activity and therefore predicting remission.

### Time to Initial Treatment

There appears to exist a 'window of opportunity' for effective treatment within early RA in adults. This window represents the time point in which the disease activity can be optimally controlled in terms of both short and long-term outcomes [290-293]. This delay may be as little as under one year [290] and the same window has been proposed in JIA, with longer time to joint injections associated with muscle wastage and disability [294]. In addition, longer time to MTX has been associated with lesser treatment response [295], with those who do not respond early having poorer subsequent outcomes [296].

**Table 7.** Summary of predictors of CID/remission from published studies

| Author (year) | Age at onset | Age at diagnosis | Female gender | Disease duration | Oligoarthritis | SES | RF + | ESR/CRP | ANA | AJC | LJC | Extra-articular features | PGA | PGE | Function | Pain/ poor QoL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Svantesson, 1983 [262] | = | | = | | | | | | | = | | | | | | |
| Pongpanich, 1988 [259] | | | | | ↓ | | | | | | | | | | | |
| Hertzberger-ten 1992 [266] | = | | = | | | | | = | = | | | ↓ | | | | ↓ |
| Gare, 1995 [255] | = | ↓ | | | ↑ | | | | | | | | | | | |
| Savolainen, 1998 [260] | | | | | | | | | | | | | | | | |
| Guillaume, 2000 [261] | = | | | | | | = | = | = | = | | | | | | |
| Minden, 2000 [264] | = | | | | ↑ | | | | = | = | | | | | | |
| Al-Mater, 2002 [267] | | | | | | | | ↓ | = | | | | | | | |
| Arguedas, 2002 [256] | = | | = | = | ↑ | | = | | = | | | | | | | |
| Kotaniemi, 2002 [268] | | | | | | | | | | | | ↓ | | | | |
| Fantini, 2003 [250] | = | | = | ↓ | | | ↓ | | | | | | | | | |
| Flato, 2003 [265] | ↑ | | = | | | | ↓ | ↓ | ↓ and = | ↓ | | ↓ | | | | |
| Wallace, 2005 [269] | = | ↓ | | | ↑ | | ↓ | | = | | | | | | | |
| Flato, 2006 [270] | ↑ and = | | ↓ and = | | | | | | | | | | | | | |
| Singh-Grewal, 2006 [271] | | = | = | | | | = | ↓ | = | = | | ↓ | | | | |
| Fernandes, 2007 [272] | = | ↓ | = | | = | | ↓ | | | | | | | | | |
| Oen, 2009 [273] | = | ↓ and = | = | ↓ and = | ↑ | | ↓ | = | = | ↓ and = | = | | ↓ | ↓ and = | ↓ and = | ↓ and = |
| Albers, 2010 [274] | = | | = | | ↑ and = | | | | = | | | | | = | | |
| Nordal, 2011 [275] | ↓CRM ↑ CR | | | | ↑ persistent | | | | = | | | | | | | |
| Berntson, 2013 [276] | | | | | | | | | | | | ↓ | | | | |
| Bertilsson, 2013 [257] | | | | | = | | = | | | ↓ | | | | | | ↓ and = |
| Huang, 2013 [277] | | | | | ↑ | | | | | | | | | | | |
| Russo, 2013 [278] | = | | | | | | | | | | | | | | | |
| Albers, 2014 [279] | = | | | | ↑ persistent | | | | = | | | | | | | |
| Berntson, 2014 [280] | | | | | | | = | | | | | | | | | |
| Guzman, 2014 [5] | | | | | ↑ | | | | | | | | | | | |
| Selvaag, 2014 [281] | | | | | ↑ and = | | ↓ | ↓ and = | ↓ | ↓ and = | | | ↓ | ↓ and = | | ↓ and = |
| Sengler, 2015 [282] | ↓ | | = | ↓ | = | | = | | ↑ | | | | | | | |
| Oliveira-Ramos, 2016 [6] | ↑ and = | | = | ↓ | = | = | = | | = | | | | | | | ↓ and = |
| Vilaiyuk, 2016 [258] | | | | | ↑ | | ↓ | | | | | | | | | |
| Alberdi-Saugstrup, 2017 [283] | | | | | | | | | | ↓ | | | | | | |
| Glerup, 2017 [284] | | | = | | | | ↓ | | = | | | ↓ | | | | |

↑: Greater values or positivity predict higher odds of CID/remission, ↓: Greater values or positivity predict lower odds of CID/remission, =: Not associated with CID/remission. CID: Clinically inactive disease, RF: rheumatoid factor, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Antinuclear antibodies, AJC: Active joint count, LJC: Limited joint count, PGA: physician global assessment, PGE: Parental global assessment, QoL: Quality of life, CR: Clinical remission, CRM: Clinical remission on medication.

### *2.5.2.1 Conclusion*

To conclude, whilst few publications have identified predictors of remission in JIA, there is a general lack of data in this area. Those factors that should be taken into account in clinical decision making likely change over the course of the JIA disease pathway. There are limitations to generalisability in the majority of studies, with retrospective, smaller cohorts using non-validated definitions of remission forming the majority of the evidence base. Inception cohorts that have explored predictors of remission have largely looked in the short-term and explored limited predictors. Overall, the vast differences in outcome definitions, length of follow-up and sparse use of multivariable analyses between studies means that it is unclear which factors independently predict validated outcomes for CID and remission in JIA at specified time points. This is particularly true for patient-reported outcomes such as pain, fatigue and quality of life. There is firstly a clear need to explore how common CID/remission are when using validated measures to assess what state is actually being measured. In addition, to limit selection bias and be able to assess predictors of CID/remission at the earliest time of intervention, there is a need to assess predictors early in the disease course in a prospective inception cohort.

**Chapter 3**

**Aims and Objectives**

# 3 AIMS AND OBJECTIVES

The overall aim of this PhD thesis is to explore the achievement of, predictors of and outcomes following fulfilment of CID and remission definitions in JIA.

Specific objectives of the thesis are:

a. Undertake a systematic literature review to describe the frequency of CID and remission in JIA.

b. To apply and compare published validated definitions of CID within a single cohort of CYP with JIA at a single time point.

c. To compare short and long-term outcomes between those who do and do not achieve CID at one year following initial presentation to paediatric rheumatology with JIA. To compare these outcomes between CYP who achieve CID according to different definitions at one year.

d. To identify clinical factors, measured early in the JIA disease course, associated with achieving remission states within three years of initial presentation to paediatric rheumatology.

# Chapter 4

# Methods

*This chapter presents the main methods used across the analyses in this thesis. The analyses are set within the Childhood Arthritis Prospective Study (CAPS), a longitudinal observational inception cohort of children with inflammatory arthritis. The chapter starts with a summary of the methods of CAPS. This is followed by a discussion of the epidemiological and analytical issues common to the analysis of longitudinal observational data. The ways in which the definitions of CID and remission were applied to the CAPS dataset are described. As this PhD is presented in journal format, the methods of each of the paper are summarised within each paper. However, this chapter also includes a more detailed description of the methods used in each paper, as appropriate. Finally, this thesis also includes a systematic review; however, the methods for this are presented within the published journal article included in section 6.1 only and are not included in this chapter.*

# 4  METHODS

## 4.1 The Childhood Arthritis Prospective Study

### 4.1.1  Overview

The majority of analyses used in this thesis used data from CAPS: a UK, multicentre, prospective inception cohort study. The overall aim of CAPS has been to investigate clinical, genetic and environmental predictors of short and long-term outcomes in CYP with inflammatory arthritides. In order to investigate this aim comprehensively, data are collected on many aspects of the CYP and their disease course. These include socio-demographic, clinical, psychological and biological data, including an untimed blood sample for genetic data and other biomarkers.

The study started recruiting in January 2001 and, at the time, represented a unique study design in JIA outcomes research. Until then, the majority of research in JIA comprised of smaller retrospective or cross-sectional cohort studies. CAPS was the first prospective inception cohort of JIA [297]. This year (2001) also corresponded with the introduction of the new international classification criteria for JIA (ILAR)[1] and with the introduction of the first biologic therapy approved for treatment of JIA (Enbrel in 2000) [118]. Therefore, the development of CAPS allowed a unique opportunity to investigate short and long-term outcomes of patients with JIA treated within this new era. Initially, CAPS recruited from only 2 centres (Alder Hey Children's Hospital, Liverpool and the Royal Manchester Children's Hospital, Manchester). In 2003, CAPS expanded to include the Royal Hospital for Children, Glasgow and the Great North Children's Hospital, Newcastle. In 2006, recruitment began at Great Ormond Street Hospital, London. The final 2 centres, the Royal Hospital for Sick Children, Edinburgh and University College London (which treats adolescents from age 12, including those transferred from Great Ormond Street Hospital) were added in 2011 and 2013, respectively. There are therefore a total of seven UK paediatric and/or adolescent rheumatology centres recruiting to CAPS (Figure 6).

When developing the protocol for CAPS, an initial target sample size of 1100 CYP was chosen. The aim of recruiting a large sample size from multiple clinics was to power subsequent analyses to investigate relatively rare exposures. For example, a sample size of 1100 is needed to detect a two-fold increase in risk for an outcome occurring in 10% of cases. This allows for exposures to affect 10% of CYP. This target sample size was

increased to 2000 CYP in 2015. This extension was needed to capture rarer exposures, such as the presence of systemic features, and relative risks smaller than two, although no specific single outcome was chosen for this calculation. To date (2018), over 1600 CYP and young people with inflammatory arthritis have been recruited.

Until 2015, the format of data collection for CAPS was based on paper-based questionnaires including a nurse review of medical records at set intervals (Figure 7), nurse-led interviews with participants and their guardians and specific questionnaires for patients/guardians to complete and mail to the study centres. In 2015, clinical data capture was moved to a web-based data collection system although patient questionnaire data remains on paper. In addition, changes to the study protocol in 2015 involved the removal of nurse interviews for logistical and cost-effective reasons. Data used in this thesis were therefore collected using a combination of medical record review and interviews by research nurses (Table 8) or directly from participants/guardians in questionnaire form (Table 11).



2003: The Royal Hospital for Children, Glasgow

2001: Alder Hey Children's Hospital, Liverpool.

2013: University College Hospital, London

2011: The Royal Hospital for Sick Children, Edinburgh

2003: Great North Children's Hospital, Newcastle upon Tyne

2001: Royal Manchester Children's Hospital, Manchester, Manchester

2006: Great Ormond Street Hospital, London

**Figure 6** Location and year of initial recruitment of centres participating in CAPS

**Figure 7.** Collection schedule for medical case note reviews, nurse and patient/guardian questionnaires for patients enrolled to CAPS.

### 4.1.2    Inclusion Criteria

CAPS aims to recruit the following CYP and young people:

i)      Onset of inflammatory arthritis before the CYP's 16th birthday

ii)     The presence of inflammatory arthritis in at least one joint

iii)    Inflammatory arthritis persistent for at least two weeks

iv)     First diagnosis of inflammatory arthritis at time of recruitment

### 4.1.3    Exclusion Criteria

i)      Septic arthritis

ii)     Haemarthrosis

iii)    Arthritis secondary to trauma or malignancy

iv)     Connective tissue disorders

These exclusion criteria aim to exclude CYP with other recognised causes of their arthritis.

### 4.1.4    Research Governance

CAPS was approved by the Northwest Multicentre Research Ethics Committee (REC/02/8/104, IRAS 184042).

After hospital consultants identify CYP eligible for CAPS, parent and age-appropriate participant information sheets are provided (Appendices). Parents can then consent their CYP into the study with the young person able to provide assent where age-appropriate (Appendices). There is then a time limit of six months for enrolling once the information sheet has been read by the parent/patient. Study nurses, who are employed at all recruiting clinics, ensure that the information sheet(s) have been understood and may answer additional questions about the study, where required.

Once a CYP has been recruited to the study, they are immediately assigned a unique study identification number. This number is then assigned to every further sample and form collected for the study. Storing and sharing of data is completed in accordance with the Data Protection Act 1998 and the University of Manchester Information Security and Data Protection Policies. Data collected as part of CAPS are stored in locked cabinets within locked offices within the University of Manchester and/or within central, encrypted networks on both NHS and University computers for paper and digital data, respectively. These latter files are password protected. Biological samples are stored in freezers within the Centre for Musculoskeletal Research within the University of Manchester. The pseudo-anonymised data are open for use by collaborators upon application if approved by the CAPS Data Access Committee with data sharing through encrypted University systems as appropriate.

### 4.1.5   Data Collection

As part of CAPS, detailed demographic, clinical, treatment, psychological and genetic data are collected from a number of sources.

#### 4.1.5.1 Medical Case Notes

Data from medical case notes are transferred to CAPS data collection forms by study nurses. The data collected from medical case notes are detailed in Table 8 and include the source of referral, features of disease, including a 75 active and limited joint count (Figure 8). This joint count includes four additional axial joints not included in the (c)JADAS71 or (c)JADAS27 scores [198,232]. Medical case note data collected for CAPS also include the results of clinical/imaging/blood examinations and medications prescribed at initial presentation to rheumatology. No aspects of clinical care were affected by a patient's enrolment to CAPS and no additional study visits to the hospital were required. Therefore, these data were only available for CAPS if completed under routine care, although centres were encouraged to record all data in the case record. Further review of medical case notes is completed by study nurses at time points detailed in Figure 7. These medical case note extractions, in addition to patient questionnaires, were initially completed at initial presentation to paediatric rheumatology, at six months, at one year and then annually to five years. However, in 2010 the requirement for six month data collection ceased and additional extractions at seven and ten years were added to the study protocol to capture longer-term outcomes (Figure 7).

Right Side     Left Side
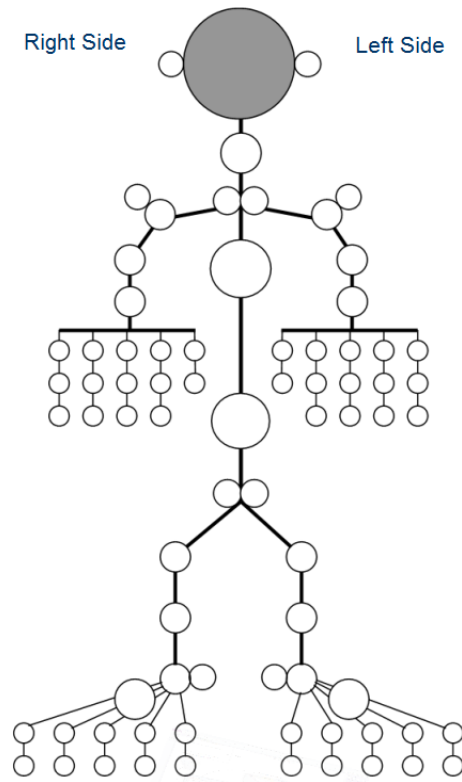
**Figure 8.** The 75 joint count used as part of the Childhood Arthritis Prospective Study

**Table 8.** Collection schedule for medical case note data

| Information group | Variable | Collection schedule* |
|---|---|---|
| Patient information | NHS number | Initial presentation |
| | Date of birth | Every follow-up |
| | Gender | Every follow-up |
| | Height | Every follow-up |
| | Weight | Every follow-up |
| Referral information | Source of referral | Initial presentation |
| | Recorded date of symptom onset | Initial presentation |
| | Results of any previous investigations | Initial presentation |
| | Diagnosis from referring physician, if recorded | Initial presentation |
| | Date of first visit to paediatric rheumatology | Initial presentation |
| Features of disease | ILAR category and revised diagnoses at follow-up | Every follow-up |
| | PGA (100mm VAS) | Every follow-up |
| | Active joint count (75-joint count) | Every follow-up |
| | Limited joint count (75-joint count) | Every follow-up |
| | Blood test investigation results if performed in standard practice (and normal range for specific hospitals): <br>• Full blood count (FBC) <br>• ESR (mm/hr) | Every follow-up |

- CRP (mg/L)
  - Normal ranges for each hospital described in Table 9.
- RF (IU/mL, cut-point <1/16 negative, 1/16 to 1/80 borderline,  >1/80 positive)
- Anti-nuclear antibody (ANA)
- Human leukocyte antigen B27 (HLA-B27)
- Immunoglobulin (Ig)

| | |
|---|---|
| • Results of any imaging studies, if performed | Every follow-up |
| Extra-articular features of disease including:<br>• Fever<br>• Rash<br>• Generalised lymph node enlargement<br>• Hepatomegaly/splenomegaly<br>• Serositis<br>• Psoriasis<br>• Nail pitting<br>• Dactylitis<br>• Enthesitis<br>• Sacroiliac tenderness<br>• Radiological sacroilitis<br>• Uveitis | Every follow-up |
| If CYP was discharged from rheumatology and reason for discharge | Every follow-up |
| Serum, cells, DNA and RNA | Single blood sample only when medically indicated or when attending for intra-articular injections, respectively. |

| Medication | | |
|---|---|---|
| | Drug name | Every follow-up |
| | Date started and stopped | Every follow-up |
| | Reason for stopping | Every follow-up |
| | Administrative route | Every follow-up |
| | Adverse reactions | Every follow-up |

*Data were extracted from the medical record at follow-up points described only if available from standard routine care and set to missing if not recorded. No additional clinical visits specifically to capture CAPS data were permitted under study ethics. NHS: National Health Service, ILAR: International League of Associations for Rheumatology, VAS: Visual analogue scale, FBC: Full blood count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, ANA: Anti-nuclear antibody, HLA: Human leukocyte antigen, Ig: Immunoglobulin, CYP: Children or young people.

**Table 9.** Ranges for normal CRP across centres recruiting to CAPS

| Hospital | Range for normal CRP (mg/L) |
|---|---|
| The Royal Hospital for Children, Glasgow | 0 to 10 |
| The Royal Hospital for Sick Children, Edinburgh | 0 to 5 |
| Great North Children's Hospital, Newcastle upon Tyne | 0 to 5 |
| Royal Manchester Children's Hospital, Manchester | 0 to 6 |
| Alder Hey Children's Hospital, Liverpool | 0 to 8 |
| Great Ormond Street Hospital, London | 0 to 20 |
| University College Hospital, London | 0 to 5 |

*CAPS: Childhood Arthritis Prospective Study, CRP: C-reactive protein

### *4.1.5.2 Nurse Questionnaires*

At initial presentation to paediatric rheumatology, patients and guardians met with study nurses to collect data not necessarily captured during routine clinic appointments. These included a detailed medical history of the participant in addition to capturing a family history of certain chronic health conditions (Table 10). Annually, study nurses met with or telephoned participants or their guardians to gain further information about any new comorbidities in addition to updated treatment and rheumatology attendance data (Table 10; Figure 7). In 2015, this additional step was removed from the study protocol as it had proved difficult to arrange and sufficient data been captured on these variables.

**Table 10.** Collection schedule for nurse questionnaires

| Information group | Variable | Collection schedule |
|---|---|---|
| Demographic data | Date of birth | Every follow-up |
| | Gender | Every follow-up, though rarely updated |
| | Ethnic group | Initial presentation |
| | Country of birth | Initial presentation |
| Family demographics | List and ages (if under 18 years) and relationships to patient of co-habiting family members | Initial presentation |
| | Guardian occupation(s) | Initial presentation |
| | Guardian income | Initial presentation |
| | Guardian age left full-time education | Initial presentation |
| | Guardian highest level of education | Initial presentation |
| Family history | Family history of autoimmune diseases | Initial presentation |
| Birth history | Details of pregnancy with patient including duration, mode of delivery, birth weight and complications as well as breastfeeding history | Initial presentation |
| Medical history | Congenital illnesses | Initial presentation |
| | Childhood infections | Every follow-up |
| | Chronic health conditions | Every follow-up |
| | Previous hospital admissions | Initial presentation |
| | Age at start of menstruation in both patient and patient's mother | For female participants over the age of 10 at initial presentation |
| | Immunisation History | Initial visit |
| History of arthritis | Age at first recalled symptoms | Initial presentation |
| | Symptoms experienced within the first two weeks and ever since symptom onset | Initial presentation |
| | Date of first GP and hospital visit with arthritis | Initial presentation |
| | Symptoms experienced at current appointment/remission status | Every follow-up |

GP: General practitioner

### *4.1.5.3 Patient/Guardian Completed Questionnaires*

In addition to data collected by nurses either from medical records or interviews with patients and their guardians, further patient/guardian-completed measures were completed. These assessed variable symptoms of JIA and its impact on the daily life of the CYP. These questionnaires were completed at the same follow-up intervals as the nurse review of medical records/telephone interviews (Figure 7).

**Table 11.** Collection schedule for patient-reported questionnaires

| Information group | Variable | Collection schedule |
|---|---|---|
| Functional ability | Childhood Health Assessment Questionnaire (CHAQ) | Every follow-up<br>Age ≤11 years completed by proxy<br>Age >11 years completed by patient |
| Wellbeing | Patient/guardian global assessment, 100mm VAS | Every follow-up<br>Age ≤11 years completed by proxy<br>Age >11 years completed by patient |
| Pain | 100mm pain VAS | Every follow-up<br>Age ≤11 years completed by proxy<br>Age >11 years completed by patient |
| Psychosocial health | Child Health Questionnaire (CHQ) | Every follow-up<br>Not completed if <8 years.<br>Age ≥8 years proxy-completed. |

VAS: Visual analogue scale, CHAQ: Childhood Health Assessment Questionnaire, CHQ: Child Health Questionnaire

### *4.1.5.4 Discharge Forms*

Where patients had been discharged from paediatric rheumatology at centres recruiting to CAPS, forms were available to provide the study team with further information. These included the date and reasons for discharge, with reasons being categorised as follows: i) Well, ii) Repeated non-attendance and iii) Transferred to another hospital. The decision to discharge from clinic was left to the treating physician and no specific remission or low disease criteria had to be met to be 'well' for physicians to make the decision to discharge, nor was it a requirement to record the current level of disease activity on the CAPS discharge form. If transferred to another hospital, further options were available to specify whether this was due to a house move, transfer to adult services or some other reason. Following discharge, although no medical case note information would be available for further collection by CAPS, participants could agree to be contacted by the study team for a further two years for nurse interviews, although in practice this unfortunately did not

often happen. In addition, participants could agree to continue completing patient-reported questionnaires as per the study schedule (Table 11, Figure 7).

### 4.1.6 Applying Criteria for Minimal Disease Activity, Clinically Inactive Disease and Remission to CAPS data

#### *4.1.6.1 Applying Wallace's Preliminary Criteria for Clinically Inactive Disease and Remission to CAPS data*

To be classified as having CID according to Wallace's preliminary criteria, one needs zero active joints, a score of 0cm on the PGA, no systemic features, normal ESR/CRP and no active uveitis [165]. The criteria are applied in the same manner regardless of ILAR category and were applied as such to all CYP in each analysis. All variables forming the criteria set are captured in CAPS. However, certain assumptions had to be made when applying the criteria set to CAPS data.

Wallace's preliminary criteria do not specify whether a full or reduced active joint count is to be used as part of classifying a CYP as in CID. As part of CAPS, a 75 active joint count is collected. This count had to be at zero to fulfil this criterion. The PGA was completed on a 100mm VAS and scores of exactly 0mm were considered as the 'best possible score' on this scale. For CYP with systemic JIA, the absence of systemic features was assumed if no fever, rash, serositis, splenomegaly or generalised lymphadenopathy were recorded in the medical case note forms corresponding with the timing of criteria application. For all CYP in other ILAR categories, this criterion was automatically met. No range for 'normal' ESR is provided with the definition of Wallace's preliminary criteria [165]. However, subsequent development of the criteria to the ACR provisional criteria defined normal ESR as ≤20mm/hour [185]. Therefore, a cut-point of 20mm/hour was used for the current analyses. For CRP, due to different assays across CAPS hospitals, limits for normal CRP differed between centres (Table 9). These centre-specific CRP ranges were used to classify 'normal' versus 'raised' CRP and were applied to CYP from each corresponding centre. Within the CAPS questionnaires, two questions were asked at each follow-up about uveitis: 'chronic uveitis' (yes/no) and 'acute uveitis' (yes/no). The absence of both of these factors was considered to represent the absence of current uveitis activity for the analyses in this thesis.

### *4.1.6.2 Applying JADAS and cJADAS Criteria for Minimal Disease Activity, Clinically Inactive Disease and Remission to CAPS data*

The formulae for JADAS and cJADAS scores have been previously described, with all joints included in the 71, 27 and 10 reduced joint counts available in the CAPS data. The scores were calculated for all CYP and cut-offs for CID and MDA applied. Summed scores were deemed to represent CID and/or MDA if falling below the previously defined cut-points [168,186] (Table 4).

Unlike Wallace's preliminary criteria, the JADAS and cJADAS apply different cut-offs for MDA according to whether the CYP has oligoarticular or polyarticular course JIA. In order to operationalise these criteria in CAPS data, CYP in the ILAR category (defined using data available at one year, replaced with data at initial presentation if unavailable) of persistent oligoarthritis were classified as 'oligoarthritis' and those with systemic arthritis, extended oligoarthritis, RF-negative or RF-positive polyarthritis were classified as 'polyarthritis'. Patients with enthesitis-related, psoriatic and undifferentiated arthritis were classified based on having fewer (oligoarthritis) or at least (polyarthritis) five active joints at one year following initial presentation, when ILAR categories were assigned.

### *4.1.6.3 Applying Magni-Manzoni Minimal Disease Activity Criteria to CAPS data*

The calculation of MDA according to Magni-Manzoni criteria has been previously described (Table 4). All 75 joints included as part of CAPS data were used to determine the active joint counts and the cut-offs for MDA applied to CYP with oligoarticular and polyarticular disease course as discussed in the previous section. Although Magni-Manzoni et al. excluded patients with enthesitis-related arthritis from their initial development process, CYP with this ILAR category in CAPS were also classified based on their number of active joints at the time ILAR category was assessed.

### 4.1.7   Patient Selection for Inclusion in Thesis

This section outlines the criteria applied to select patients for inclusion to each of the main analyses presented in this thesis. The CAPS cohort continued to recruit and capture follow-up data over the duration of this PhD and some analyses required longer periods of follow-up than others. It was therefore decided that, rather than use a single cohort for all papers, the cohorts would be updated using specific inclusion criteria for each paper, based on the underlying research question addressed. The specifics of selection criteria for each analysis are presented below under the title of each paper.

### 4.1.7.1 How Common is Clinically Inactive Disease in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis? The Importance of Definition

The first paper using CAPS data (Section 6.2) aimed to quantify how many CYP with JIA achieved CID at one year following initial presentation to paediatric rheumatology. To this end, patients were included if they had a physician's diagnosis of JIA and were recruited prior to December 2013, to allow for at least one year of follow-up to April 2014, the date at which the analysis was commenced. Patients were excluded from this study if no study forms had been returned. A further decision was made to exclude prevalent cases of JIA, defined pragmatically as having been prescribed a biologic therapy prior to their first visit to paediatric rheumatology at a CAPS centre. Although CAPS is an inception cohort, it became evident that a very small number of patients did not have a new diagnosis. On review of these cases it was clear that although new to the CAPS centre they had been diagnosed elsewhere and had moved to a CAPS centre and as such did not have a new diagnosis of JIA. No other restrictions were placed on patient selection.

The currently published definitions for CID and/or MDA have not been validated in enthesitis-related, psoriatic or undifferentiated JIA. Systemic JIA-specific JADAS and cJADAS measures have also not been developed [168,186]. However, in order to gain an understanding of CID/MDA achievement across all categories of JIA, and compare these estimates with published evidence, this paper included all CYP with JIA registered with CAPS regardless of ILAR category.

### 4.1.7.2 Long term Outcomes Following Achievement of Clinically Inactive Disease in Juvenile Idiopathic Arthritis: the Importance of Definition

The second paper using CAPS data (Section 6.3) focused on the short and long-term outcomes following achievement of CID and MDA at one-year. Long-term outcomes were assessed to five years (four years after determination of MDA/CID) following initial presentation to paediatric rheumatology. Therefore, to allow for at least five years of follow-up, patients were selected from CAPS if diagnosed with JIA and recruited prior to 1st January 2011. Patients who had no outcome data at any follow-up visit relating to any of the outcomes studied within the five year follow-up window were excluded.

As previously mentioned, with the exception of Wallace's preliminary criteria for CID, which includes systemic features, no other CID/MDA criteria exist for ILAR categories which include extra-articular features as part of their classification criteria. As these extra-articular features may also influence long-term outcomes, a decision was made to limit this

paper to only the oligoarticular and polyarticular ILAR categories. Therefore, for this paper, the inclusion was limited to patients with oligoarticular, RF-negative or RF-positive polyarticular JIA only.

### 4.1.7.3 Factors Associated with Remission in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis: the Importance of Definition

The final paper using CAPS data included in this thesis focused on factors associated with remission in JIA (within the first three years). Therefore, to allow for at least three years of follow-up, patients were selected if diagnosed with JIA and recruited prior to 1st January 2014. Again, patients with no returned study forms were excluded and the paper was limited to those with oligoarthritis, RF-negative or RF-positive polyarthritis.

## 4.2 Epidemiological Considerations

Observational cohort studies, such as CAPS, face many epidemiological challenges including selection bias, confounding as well as attrition and missing data. This is particularly a problem when data capture continues over a number of years. This section outlines some of the main epidemiological considerations faced within the PhD, including ways that their impact was minimised or handled within CAPS.

### 4.2.1 Selection Bias

#### 4.2.1.1 The Principles of Selection Bias

Selection bias generally refers to whether patients involved in a study are truly generalisable to those in the general population of those patients [298]. If the study population and general population of patients are similar, the results of the study will likely have external validity [299]. External validity, the ability to generalise associations to different samples, settings and times [300], is vital in the comparison of results across studies and the application of these new evidences in the target population. The sampling and follow-up strategies for a given study determine the likely impact of selection bias, including from where, and how, eligible patients are selected and at what point in their disease course.

#### 4.2.1.2 Locations for Patient Selection

A pragmatic method of recruiting patients with rarer diseases requiring specialist care is from a hospital setting. Recruiting through primary care practices or community settings would require immense resources to recruit few patients. However, recruiting from a single hospital may introduce selection bias. Hospitals may be located in very different geographic and socioeconomic areas. Patients could differ in terms of ages, ethnicity,

socioeconomic factors, and distance to their nearest healthcare professional [301]. Therefore, results gained in a single centre may not generalise to the larger population of patients with the condition of interest. To mitigate this selection bias, multiple hospital sites can be used. This bias may be reduced further when implementing population-based studies, which may include all clinics within the population of interest, rather than a selection of clinics which may still contain a biased sample.

Since JIA is a rare disease requiring specialist care [27], the decision was made to recruit patients for CAPS from paediatric rheumatology centres. This allowed for a greater concentration of patients with JIA across recruiting sites. Recruiting from multiple areas across England and Scotland allows CAPS to select a relatively representative cohort of patients with JIA across Great Britain, but notably excludes Northern Ireland and Wales (with the exception of Northern Wales where patients may attend hospital in Liverpool).

Even when recruiting from all clinics within a defined area, selection bias may still occur against 'hard to reach' patient types. These could include patients who are less likely to be referred to secondary care and those less likely to be recruited into a study once referred even if eligible. Many factors contribute to both of these forms of selection bias, for example, isolated communities who are less able to attend clinics/studies, non-English speakers, patients with such severe disease that they cannot participate and patients with mental health problems including learning difficulties who would not be able to truly provide informed consent [302-305]. In addition, patients from poorer socioeconomic backgrounds or ethnic minorities are known to be difficult to recruit to studies and to present to clinical appointments [103,306]. Where hard-to-reach patients are not included in clinical research, results produced may not be externally valid in these populations. Therefore, studies recruiting from multiple hospital settings may not always capture or generalise to the entire target population.

CAPS is set within the UK NHS, a universal healthcare system. Therefore presentation to clinic appointments may be less of a barrier to patients from poorer socioeconomic backgrounds. Whilst geographically isolated patients may attend specialist services if their disease is severe and requires hospital treatment, those with milder disease may choose not to be referred into secondary care. In terms of recruiting eligible patients who do attend clinic appointments, other hard-to-reach patient groups may have been accessed successfully in the UK e.g. non-English speakers have NHS translators provided; however other barriers such as patients or families with mental health disorders have not been explored. Whilst CAPS therefore aims to capture many hard-to-reach patient groups, the

coverage is partially limited. However, the sampling methods once patients present to clinic appointments minimises the risk of selection bias.

### 4.2.1.3 Sampling Methods

After selecting recruiting centres, multiple methods are available to select patients. The simplest but most biased sampling technique is convenience sampling. In convenience sampling, a group of patients undergoing a specific intervention is selected, e.g. a study in synovial fluid biomarkers from patients undergoing steroid injection to the knee [307]. Selection bias is introduced where patients with the disease of interest do not have an equal chance of recruitment. Greater external validity is gained in consecutive or random sampling techniques [308]. For the former, every eligible patient passing through the clinic within a given time frame is selected for the study [308]. For the latter, a random sample of these patients is selected [309]. However, in a rarer disease or when studying a rare outcome, every eligible patient may be of interest.

Patients participating in CAPS have been recruited consecutively. Every patient that meets the inclusion criteria are approached at the point of initial presentation to paediatric rheumatology. This allows all eligible patients to be approached within the recruitment time frame.

When recruiting patients using any of the previously discussed methods, a decision is made regarding whether patients with new or recently-diagnosed disease versus prevalent disease should be eligible for inclusion. CAPS uses an incident case design. Inception cohorts recruit patients from the initial presentation of the patient with their disease of interest [310]. In contrast, prevalent sampling excludes eligible patients who have been previously followed and dropped-out at recruiting centres (also referred to as left censorship). This left censorship is therefore minimised in the CAPS study design.

## 4.2.2   Confounding Bias

### 4.2.2.1     The Principles of Confounding

In clinical trials, patients are randomised to various exposure and/or control arms. It is therefore likely that patient characteristics are balanced between different arms of the trial [311]. Associations between exposures and outcomes will, therefore, not be distorted by these characteristics. In observational research, comparing the effect of an exposure (e.g. CID), with an outcome (e.g. functional ability), may be biased by 'confounders'. Confounding is illustrated in Figure 9.a. A confounder is associated with both an exposure and the outcome of interest, without lying on the causal pathway [312]. Where the variable does lie

on the causal pathway, it is called a mediator (Figure 9.b) [312] and where an interaction exists with a variable affecting the strength of the association, it is moderator (Figure 9.c). Measured or unmeasured confounders that are not appropriately accounted for when assessing associations can dramatically affect the direction or size of the association observed. An example of confounding could be an association between gender and disease activity in JIA, which is confounded by ILAR subtype. The male: female ratio is highest for systemic and enthesitis-related JIA, two of the most severe forms of the disease [4,31]. Without controlling for ILAR subtype, a result that males have higher disease activity than females could be found and may be misleading. However, there are multiple analyses that can take this association into account. Each requires the confounder to have been measured as part of the study; other than randomisation in a trial setting, there is no widely accepted method to address unmeasured confounding. Approaches to account for confounders include restriction, stratification and adjustment in regression models.
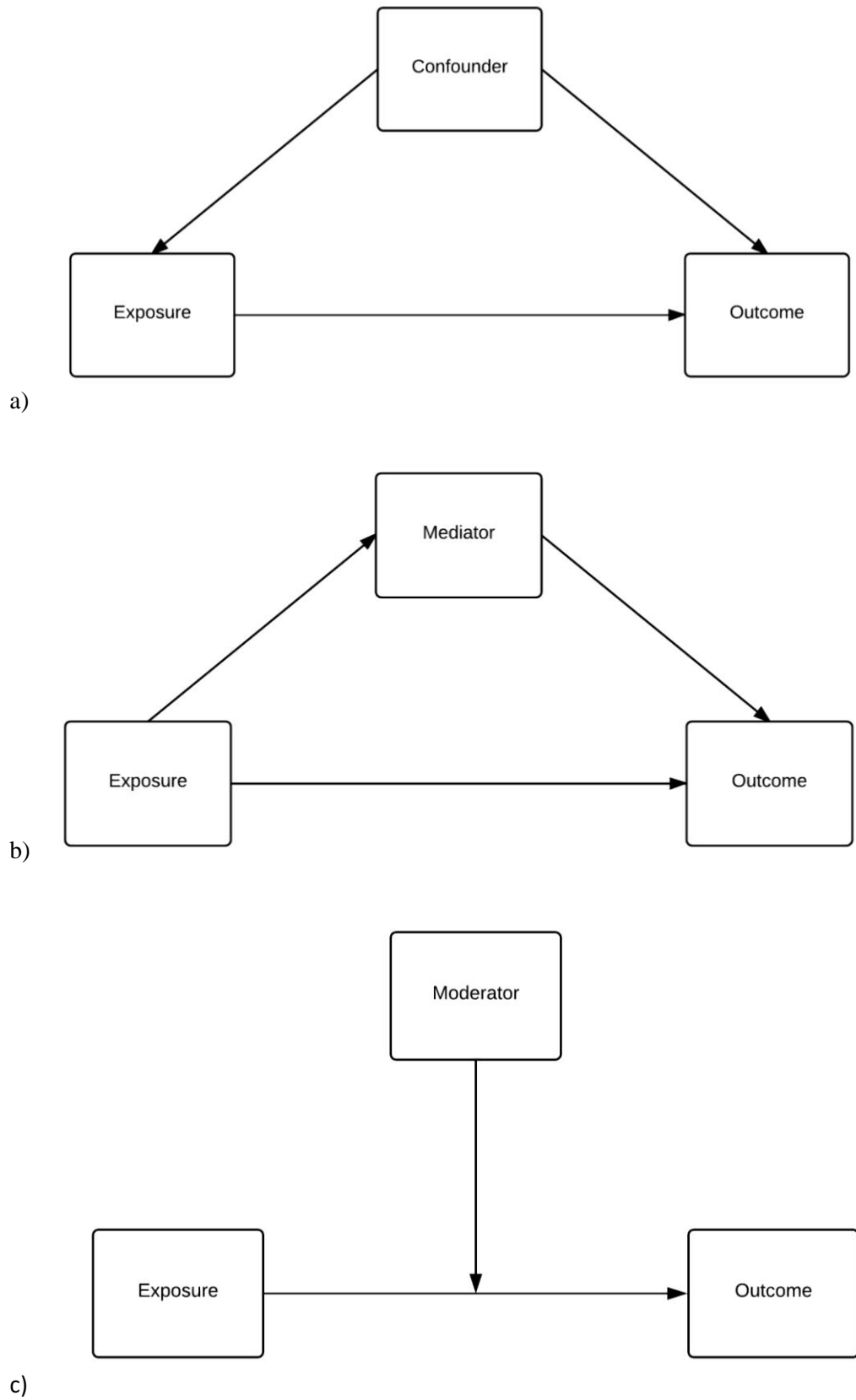
**Figure 9.** a) Association with a confounder, b) Association with a mediator, c) Association with a moderator

### 4.2.2.2 Restriction

If only a specific subset of CYP, based on a value of the confounder, are of interest, the dataset can be *restricted* to this subset [312]. For example, if an association between a particular exposure and remission is only relevant to certain ILAR categories, the analysis can be restricted to only CYP with these categories. Whilst this analysis effectively controls for confounding, power may be limited and results will not be generalisable [312] outside of the restricted population, e.g. selected ILAR category. Since remission criteria for the final two analyses in this thesis are not strictly applicable to ILAR categories other than oligoarticular and both polyarticular JIA categories, these analyses were restricted to these three categories.

### 4.2.2.3 Stratification

Stratification to mitigate confounding is only possible for categorical confounders of interest, or where continuous confounders can be split into categories. After stratification, results are compared within or across groups [311]. For example, the association between exposure and remission could be compared between individual ILAR categories.

Stratification allows the investigation of associations between exposures and outcomes for different strata. This could be reasonable in a dataset including CYP with three autoimmune conditions: JIA, lupus and asthma, stratifying these models based on distinct conditions may be preferable due to i) Different relationships between the condition with other variables of interest (i.e. potential interactions), ii) Different clinicians treating the conditions who would want to know the effect in a specific condition.

Although stratification may produce clinically meaningful results for the groups in question, there are limitations in terms of study power. Study power relates to the probability of detecting an effect when there is a true effect to be detected i.e. the probability of not having false negative results. This power increases with increasing sample size, with greater variability associated with fewer participants [313]. The process of stratification splits patients into smaller groups and, thus, when the number of confounder categories increase, statistical power can be severely limited [311]. Finally, the resulting associations are only applicable to individual subsets of CYP analysed and cannot be generalised to entire study populations. Thus, clinical applicability to heterogeneous study populations is decreased. For the current thesis, analyses were stratified by ILAR category where assessing risk factors for remission, where it was likely that different predictors of remission existed between these disease categories.

### *4.2.2.4 Adjustment*

The most widely used method to control for confounding bias in health epidemiology is adjustment within a regression model [312]. Rather than running individual models for each confounder category, all subjects are analysed in the same model. The equation for a basic linear model with a single confounder is illustrated in Equation 5 where $X_1$ is the variable of interest and $X_2$ the potential confounder. Betas ($\beta$) reflect the size of the associations between their respective $X$ and the outcome $Y$.

$$Y = \alpha + \beta_1 x_1 + \beta_2 x_2 + c \qquad (5)$$

The value of the potential confounder(s) is held at a constant level, thus the independent association between the variable of interest and the outcome can be assessed. Unlike stratification, where the confounding variable is split into multiple categories, with no regard to how the strata are related, adjusting assumes a linear relationship between the outcome and confounder [314]. Adjustment has the benefits of estimating associations independently of a confounder in an entire study population and can be expanded to include multiple confounders in a multivariable model, e.g. Equation 6, where $X_2$ to $X_n$ are potential confounders. This analysis not only allows the gain of point estimates for association between the explanatory variable of interest and the outcome, but also the confounding variable(s) and the outcome; however, the number of confounders that can be added to the model is limited.

$$Y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_n x_n + c \qquad (6)$$

The number of potential confounders to include in a regression model is limited by the number of observed outcome events. A general rule of thumb is that around 10 events per additional variable are sufficient for binary outcomes [315,316], with at least two participants per variable required for accurate estimation of coefficients and confidence intervals for continuous outcomes [317]. In large observational datasets, there may be many items that may be considered as potential confounders in a regression model. Methods therefore need to be undertaken to limit the number of variables.

### *Limiting the Number of Covariates for a Regression Model*

At the initial stage of regression model development, variables that have any of the following characteristics may be excluded from consideration in the model i) There is no plausible clinical association with the outcome, ii) They are unfeasible to collect in the target population iii) There are high quality studies showing no association with the

outcome [318]. Once variables that are unfeasible to collect or unlikely to add to the model have been excluded, there may remain a large pool of potential variables for inclusion.

The next stage of variable selection does not take the outcome of interest into account. Considering the resulting pool of potential covariates, those that are highly correlated or associated with another potential variable may be excluded from consideration [319]. Those that have greater missing data or are less feasible to collect could be excluded [320]. Once the pool of potential variables has been reduced to those that are clinically relevant, feasible to collect in the target population and not collinear with other variables, there may be few enough to force into a multivariable model with no further selection methods. This is the simultaneous entry method [319].

Simultaneous entry methods are favourable in terms of clinical relevance [319]. However, because no statistical techniques were used to select the variables, there may be covariates in the model that do not explain variation in the outcome and thus model fit may not be optimal. Alternative, purely statistical methods for variable selection include univariable screening and stepwise methods [318] [319]. However, these methods are more appropriate when developing prediction models rather than assessing risk factors for particular outcomes. Thus, neither technique was employed in this thesis.

### 4.2.3    Missing Data

#### 4.2.3.1    Types of Missing Data

When studying cohorts of patients, there is invariably a high risk of missing data. These missing data could relate to exposure, outcome or confounder data. This is particularly evident in observational data [321], where patients are receiving standard care. These patients may not present to clinical appointments for a number of reasons, such as inconvenience, accidental omission, but also in relation to their current symptoms, whereby patients who are well may choose not to attend. In JIA, CYP in remission off medication are often discharged from continued rheumatology care. Alternatively, patients may attend clinical appointments but may not have all outcome measures completed and/or recorded in their medical record as part of their clinical assessment. This reflects clinical practice, whereby a physician may tailor their examination or assessments based on the symptoms of the patient. In busy outpatient clinics, there may not be the opportunity to record all variables due to time pressures. For JIA, assessments that may not be completed in every appointment include those requiring a blood sample. These samples are usually only taken when clinically indicated due to the stress of the procedure, particularly in younger CYP

[157]. Although missing data can therefore take on multiple different forms, it is important that the pattern of missing data is identified and the impact on the study assessed. Three different patterns of missing data may be observed.

### Missing Completely at Random

Missing data are missing completely at random (MCAR) if the probability of missingness does not depend on any measured or unmeasured data collected in a given study [322]. For example, if a batch of patient reports were lost in the post on the way to the study centre, these data are MCAR.

### Missing at Random

Data are missing at random (MAR) if the probability of missingness depends on observed data i.e. that has been measured in the study [322]. For example, certain clinicians may be more fastidious when completing the PGA during assessment of their patients with JIA and some may be less so. The values of missing PGA scores may be similar to available scores, with missingness purely depending on which clinician assessed their disease activity.

### Missing Not at Random

Data are missing not at random (MNAR) if the probability of missingness is dependent of the values of the missing data [322]. For example, CYP who are in no pain may not present to clinical appointments. Therefore, data available for pain would represent a group of CYP with higher pain than the entire cohort. It is possible for data to be both MAR and MNAR, for example where missing values of pain may be higher, but other measures of outcome which correlate with pain have actually been recorded.

#### 4.2.3.2    Testing for Missing Data Types

Whilst it is impossible to definitively confirm missing data types, it is possible to infer the most likely type through a combination of statistical tests and biological plausibility.

The difference between data MCAR and MAR is an association between missingness and observed data. This association can be tested in an existing dataset through logistic regression analyses with observed variables as explanatory variables and a binary missingness variable (0: present, 1: missing) used as the outcome for the variable of interest. If associations between any of the potential explanatory variables and the missingness variable are present, then data are not MCAR.

Statistical testing for data MNAR is more challenging without sampling a subset of patients with missing data to gain more information about why their values are absent. Previous data may be used if they are lost-to-follow-up, for example where CYP with JIA who have lower disease activity are more likely to be lost-to-follow-up [250]. In existing data, the only option to test for data MNAR is to construct a similar model to that described previously, however using a proxy, potentially collinear, variable as the explanatory variable. For example, ESR and CRP are both acute phase reactants and therefore both measure inflammation [157]. If a CYP had a value for ESR and not CRP, a logistic model could be constructed with missing CRP (yes/no) as the outcome and continuous ESR value as the explanatory variable. If an association was observed, for example lower ESR is associated with missing CRP, CRP data may be considered MNAR; Lower CRP values are more likely to be missing. However, in this example, data are also MAR as associated with ESR: As previously stated, the latter two missing data categories are not mutually exclusive. Although analysing these data would therefore be possible, in the presence of a more complete collinear variable, the most reasonable analysis plan would involve the use of the more complete variable. In some cases, incomplete data may introduce bias in associations between available exposures and outcomes. In these cases, methods to mitigate this bias may be required.

### 4.2.3.3    Missing Data Bias

As previously discussed, not including a representative sample of patients in a study can result in a lack of external validity [299]. However, if a representative sample is included in the study, but only those with complete data are included in the analysis, internal validity may additionally be affected. Internal validity relates to whether the results of the study are true for the study population [300]. The effect missing data may have on this internal validity can be judged based on the type of missing data [323].

#### Missing Completely at Random
MCAR data do not bias association point estimates in analyses.

#### Missing at Random
Conversely to data MCAR, MAR data can bias associations. The direction of bias depends on whether subjects with available data are more or less likely to achieve the outcome of interest. Using an earlier example, if the fastidious clinician worked in a hospital that was generally referred more severe cases than other hospitals, CYP with available PGA scores may be less likely to achieve remission than those with missing PGA values. Therefore,

the association between PGA score and remission may appear to attenuate compared with an analysis with complete data.

### Missing Not at Random

Data which are MNAR invariably bias point estimates if not accounted for and similar to data MAR, this bias could be in either direction. Using the previous example of CYP with lesser pain not presenting to clinical appointments, the use of this dataset to study associations between pain and remission would result in biased estimates. The association between pain and remission would be attenuated if the missing data were not accounted for, since those with low pain, and therefore likely higher remission rates, would be missing. In the latter two types of missing data, methods are therefore needed to mitigate potential missing data biases.

#### 4.2.3.4 Statistical Methods to Mitigate Missing Data Bias

For all data types, excluding patients from analyses will reduce the study power to detect differences between subgroups of patients. This reduction in power occurs through a reduction in sample size with a resultant decrease in the precision of estimates (observed through wider intervals of variance e.g. 95% CI around any point estimate) [324]. However, to limit bias of point estimates, a number of techniques can be employed which are increasingly complex when considering MCAR to MNAR data.

Before any methods are implemented to infer or exclude missing data from analyses, their impact on the study question should be tested. If techniques to infer missing values would make no clinically meaningful difference to the results, there is no value in inferring them.

### Complete Case Analyses

Complete case analyses involve analysing only the data that are present in a given dataset. This means that any patients who are lost-to-follow-up will be excluded from the analysis if data following their loss from the study are required. However, those that attended but have incomplete data in the variables of interest are also excluded [325].

If the only data missing are MCAR, or they are MAR but do not relate to the outcome of interest, unbiased associations will be produced [326]; in these cases, only estimates of variability i.e. width of confidence intervals are affected. However, if missing data are MAR and relate to the outcome or data are MNAR, complete case analyses will result in biased point estimates in either direction.

Since complete case analyses are used widely in the literature, these analyses are often necessary to compare across publications, despite the variability in both internal and external validity for different data types. In addition, comparison of results following complete case versus analyses accounting for missing data allows an assessment of bias in this preliminary analysis.

## Most Extreme Scenarios

To test the potential impact of missing data, a minimum/maximum analysis can be undertaken [325]. In this analysis, all missing data are initially set to their minimum possible value and the planned analysis is completed. Following this, all previously missing values are set to their maximum possible value and the analysis undertaken for a second time. Results from these two analyses can then be compared with those from a complete case analysis. If there are no clinically important differences, decided based on published minimal clinically important differences (MCID) in outcomes or clinical expertise, a complete case analysis should suffice. This analysis is the most straightforward for binary or ordinal missing variables where minimum and maximum values may be clinically plausible [325]. For continuous variables, setting minimum and maximum values may not be plausible [325] e.g. despite the minimum score of zero being common on the CHAQ, it is very rare for CYP with JIA to achieve a maximal score of 3 [212]. In these cases, minimum/maximum analyses may not prove valuable [325]. For binary or ordinal outcomes, however, where a clinically important difference is observed between the minimum and maximum scenarios, imputation methods may be implemented.

## Single Imputation

Single imputation involves inferring the value of a missing value from observed data in a given dataset. There are various imputation methods that can be used to infer these values, with the common theme that a single value is inferred. Common examples of single imputation include replacing missing values with the mean, or median, of observed values, or bringing forward the last observable value to replace the missing data point [327]. There is a potential limitation of too precise estimates in all single imputation methods: the potential value for a given missing data point falls within a distribution of likely values. Imputing a single value and assuming it has the same accuracy as observed values therefore leads to underestimations in measures of variability, where different estimates may have been produced if the analyses had been repeated [328].

### *Last Observation Carried Forward*

Last observation carried forward (LOCF) analyses are often used in longitudinal studies. If missing data arise over time, LOCF analysis would replace missing values with the most recent non-missing values from earlier in follow-up [325]. This has the benefit of being simple to complete and the ability to use all patients in the analyses, regardless of whether they have incomplete data.

LOCF analyses are commonplace [329] but assume that patient outcomes remain stable over time and do not improve or decline [330] despite potential changes in treatments, their reasons for having missing data and the natural life-course of the disease. This analysis can therefore result in biased point estimates for associations across all three missing data types, with too precise measures of variation.

### *Multiple Imputation*

Multiple imputation involves the use of available data to infer the values of missing observations, generating multiple potential values for the missing variable. In this way, estimates are not biased for data MAR as they are based on other available data. In addition, variance estimates are not underestimated since multiple values are generated per missing data point [331].

There are various methods for multiple imputation, with the initial decision based on the missingness pattern in the dataset to be analysed. There are broadly two patterns of missingness: monotone or non-monotone [332]. A monotone missingness pattern assumes that once a missing value has arisen, all further values will also be missing. Similarly, if a value is present, it is assumed that all previous values are also present [332]. Therefore, in a longitudinal cohort like CAPS, the only CYP who may have monotone missingness are those lost-to-follow-up who do not return to the study. However, if they previously had incomplete data during their follow-up, their missingness pattern is no longer monotone. Conversely, CYP with non-monotone missingness may have different incomplete variables at various follow-ups with no particular pattern.

Multiple imputation methods differ for monotone or arbitrary datasets (those that contain both monotone and non-monotone data). Since the former data structure is not feasible for longitudinal cohorts, only multiple imputation methods that were applicable for arbitrary missingness-patterned datasets were considered for this thesis.

## Multiple Imputation: a General Approach

Regardless of imputation approach, the broad structure of multiple imputation remains the same. The first step is to use existing data built into an imputation model to estimate missing values. This is completed '*n*' number times, or over multiple iterations, until '*n*' datasets are filled with complete data. The analyses are then run in each of these datasets and results pooled using Rubin's Rules, whereby a coefficient of interest $\beta_{MI}$ is the mean of observed coefficients $\hat{\beta}$ over imputed datasets *m* (Equation 7).

$$\beta_{MI} = \frac{1}{m}\sum_{i=1}^{m}\hat{\beta}_i \tag{7}$$

To calculate a measure of variability, Rubin's Rules calculate total variance for the estimate *T* (Equation 8), accounting for both within, (Equation 9) and between (Equation 10) imputation variability, *W* and *B*, respectively [332,333].

$$T = \overline{W} + \left(1 + \frac{1}{m}\right).B \tag{8}$$

$$\overline{W} = \frac{1}{m}\sum_{i=1}^{m}W_i \tag{9}$$

$$B = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{\beta}_i - \overline{\beta}) \tag{10}$$

No current rules exist for how many datasets to impute for the most accurate and unbiased estimates following the pooling of results. Published recommendations suggest as few as three to five imputed datasets are sufficient once the model has reached convergence [334]. Alternative methods have been suggested based on the fraction of missing data [335]. However, these latter approaches also suggest that after a small number of datasets have been generated, the gains of imputing further estimates drastically diminish [335]. There were unbiased estimates of regression coefficient values produced over different numbers of imputed datasets, ranging from n=3 to n=100, regardless of the proportion of missing data [336]. The multiple imputation technique employed in this thesis used an empirical 20 imputed datasets and allowed different outcome variable types to be imputed at the same time using different types of regression model: multiple imputation using chained equations.

## Multiple Imputation using Chained Equations

One of the more flexible approaches to multiple imputation is that using chained equations [331]. This method does not assume that all variables included form a joint normal distribution, an assumption which may be unlikely in large observational cohorts. Uniquely, the entire set of variables due to receive/inform imputed data do not have to

form part of one, large model. Instead, each variable is modelled separately using its distribution, for example a continuous variable such as ESR could be modelled according to a linear regression and binary variables such as remission modelled using logistic regression models. For each of these models, the entire list, or a subset of, variables may inform these missing values. The steps of multiple imputation using chained equations can be summarised as follows [331]:

1. Every missing value in the initial dataset is inferred using a single imputation technique (e.g. taking the mean of available data for that variable).

2. For the first variable, its single imputation values are returned to 'missing'. Missing values are then inferred using their specific regression imputation model that may or may not include all variables in the dataset.

3. Single imputation values for the second variable are then returned to 'missing'. Missing values are inferred using other variables including newly imputed values for the first variable.

4. Steps two and three are repeated until all variables with missing data have imputed values based on other variables that were not completed using single imputation methods. This marks the end of the first iteration.

5. Steps two and three are then repeated over multiple iterations until stable estimates are produced.

6. Analyses are then completed in each separate iteration and results pooled for a final result, complete with measures of variation i.e. standard errors.

Although a more flexible approach to multiple imputation, multiple imputation using chained equations still holds various assumptions, which if violated could bias the estimates gained.

*Assumptions of Multiple Imputation using Chained Equations*

The first assumption of multiple imputation using chained equations is that any variable to be analysed for the research question must be included in the imputation model. If important variables, for example predictors to be tested against a given outcome, are excluded from these models, an assumption is placed that these variables are not associated with the outcome of interest. After imputing missing data, the predictor that was excluded from the imputation model may therefore appear to have no relationship with the outcome. Care must therefore be taken to include all relevant variables to the missing values of interest into the imputation model, including the outcome [331]. This may include variables that may not relate directly to the study question.

An additional benefit to multiple imputation using chained equations is that the imputation model is not assumed to be exactly reflective of the analysis model in terms of the variables included [331]. Auxiliary variables, those that may not be related to the research question but may be informative for the probability of missingness or imputing missing values for other variables in the model, may also be included in the imputation models [337]. The limitation to this is that only a certain number of variables may be included for the purposes of statistical power. The benefit of multiple imputation using chained equations is that certain auxiliary variables may only inform a select number of variables needed to impute. In this case, these auxiliary variables may be included only in the imputation equations with related variables as the outcome. Each variable, auxiliary or otherwise, may take a different form and may therefore require different types of regression model to be imputed.

As previously mentioned, imputation equations under multiple imputation using chained equations make take various forms. Whilst this is a highly flexible approach, assumptions of the individual regression models apply. These assumptions are detailed in a later section.

A final assumption of multiple imputation using chained equations is that missing data are MAR [325,331]. This method infers missing values from measured data and does not account for data missing according to other mechanisms. This is problematic where data are likely MNAR.

*Multiple Imputation Sensitivity Analyses for Data Missing Not at Random*

Since multiple imputation using chained equations assumes data are MAR, alternative methods need to be undertaken to account for the potential MNAR pattern. Sensitivity analyses can therefore be completed under different clinically plausible assumptions about the values of missing data. This may take the form of raising or lowering imputed values by a fixed value or measure of variation e.g. one standard deviation higher [338]. To inform this, one might seek clinical advice on the likely values in patients with missing data. However, these values may also be biased based on the anecdotal evidence within this expert opinion.

Following sensitivity analyses, the results can then be compared to those from the MAR analysis. The benefit of these sensitivity analyses is in accounting for clinically plausible missingness mechanisms not possible under standard imputation methods. However, distinctly different results may be gained depending on which clinical assumption is placed

on the models. In addition, altering imputed values by a measure of variation may not truly take clinical judgement into account. However, imputing a single value based purely on clinical judgement leads to overestimates of precision, similar to other single imputation techniques.

## 4.3 Statistical methods

This section outlines some of the overarching statistical principles that were applied in this thesis, common to all analyses, followed by a more in depth discussion of the statistical methods applied to each CAPS results paper.

### 4.3.1 Descriptive Statistics

Descriptive statistics are useful for a broad understanding of a particular study population or subgroup before any analyses are undertaken [339]. For normally distributed continuous variables, the mean can be described alongside the standard deviation as a measure of variation. For non-normally distributed continuous variables, the median is a measure of central tendency less affected by outliers, with interquartile ranges (IQR) describing bounds for the central 50% of the data [339]. Categorical variables can be described using frequencies or proportions [340].

### 4.3.2 Regression Modelling

Regression analyses allow for the quantification of both point estimates for associations, but also a measure of confidence around these estimates: confidence intervals (Equation 11). These are defined by a particular percentage based on a number of standard deviations from the mean point estimate within a sampling distribution. For example, 95% of data in a normally distributed sample is captured within 1.96 times the standard deviation either side of the mean. If this sampling distribution were sampled repeatedly with replacement (i.e. whereby sampled values are placed back into the dataset before taking the next sample), the point estimate gained from the regression analysis would be expected to fall within these upper and lower bounds 95% of the time.

$$\bar{X} \pm 1.96 \frac{\sigma}{\sqrt{n}} \tag{11}$$

There are various types of regression model available which differ based on types of covariates, outcomes and relationships assumed. The models used in this thesis include generalised linear models: linear, logistic and negative-binomial models with modifications when assumptions of these models are not met.

## *Linear Regression*

A basic linear model can be used to detect and quantify associations between a continuous or categorical exposure and a continuous outcome [341]. They follow the basic equation presented in Equation 12.

$$y_i = \alpha + \beta x_i + c_i \tag{12}$$

In the above linear model, for person $i$, $Y$ is the outcome and is based on a magnitude $\beta$ of exposure $X$ plus an intercept value $a$ and error $c$. For continuous variables with continuous outcomes, $\beta$ is described according to one increasing unit of the independent variable. As the intercept value, $a$ represents the value of $Y$ when there is no association between the exposure and outcome (i.e. $\beta = 0$). The model can be adjusted to include multiple potential confounders.

## *Logistic Regression*

Binary logistic regression models (Equation 13) are appropriate when the outcome is binary e.g. remission or no remission [342].

$$log \left( \frac{p(event)}{1-p(event)} \right) = \alpha + \beta x_i + c_i \tag{13}$$

For binary logistic models, $\beta$ is interpreted as the log of an odds ratio, which can be exponentiated to give the value of the ratio itself. A basic example of calculating an odds ratio can be observed through comparing the odds given in Table 12 using Equation 14. In place of the value of the outcome increasing by one independent variable unit, odds ratios from logistic models are interpreted as the increase in odds of the outcome associated with one unit of this increase, or against a referent category [342].

**Table 12.** A 2x2 Contingency table

|  | Experienced outcome | Did not experience outcome | Odds of outcome for each exposure group |
|---|---|---|---|
| Exposed | a | b | a/b |
| Not exposed | c | d | c/d |

$$OR = \frac{Odds\ of\ outcome\ if\ exposed}{Odds\ of\ outcome\ if\ not\ exposed} \tag{14}$$

## Regression Models for Count Data

The final types of regression models used in this thesis model count outcomes. The basic model for count data is a negative binomial regression model (Equation 15) [343]. The value of $\beta$ for these models is interpreted as the increase in log count for every unit of the explanatory variable. For example, for each increased year of age, the log count for the number of active joints increases by the coefficient value. Alternatively, incident rate ratios can be produced, which are interpreted as the percent change in the outcome for every increased unit of the explanatory variable. These models can also incorporate categorical predictors, the associations for which are interpreted as the increase in log count (coefficient) or percent (incident rate ratio) compared with the reference category. A specific form of negative binomial model is the Poisson model. However, these models are only appropriate when the variance of the data is equal to the mean, i.e. there is no over-dispersion [343]. If data are over-dispersed, Poisson models can produce standard errors that are too small, compared with negative-binomial models which incorporate an over-dispersion parameter [344].

$$log(y) = \alpha + \beta x + c \qquad (15)$$

Although negative binomial regression models can incorporate data which are over-dispersed [343], they do not address the cause of the over-dispersion. One common cause is the presence of excess zeros [345]. For count data with excess zeros, the zero values are often generated by a separate process to increases in non-zero values [345]. A zero-inflated negative binomial model splits data based on the outcome count value. Initially, it models a binary logistic regression, producing odds ratios for having an outcome count of zero or non-zero. Secondly, it models a negative-binomial regression model against the non-zero counts, producing coefficients or incident rate ratios as previously discussed.

## Assumptions of Regression Models used in this Thesis

All regression models hold certain assumptions regarding, for example, the distributions or independence of the data modelled. The assumptions tested for regression models used in this thesis differed between the linear, logistic and negative-binomial models. These models share some assumptions: independently distributed data, no interactions and no collinearity (Table 13).

Assumption 1: The data are independently distributed

The first assumption of linear, logistic and negative-binomial regression modelling is that the data are independently distributed (Table 13). Regressions models require that each variable comes from a single, independent participant and therefore data are not clustered in any way. However, in clinical settings, patient data are often clustered. A cluster is defined by a group with a common factor. Patient data, for example, cluster within individual patients. In a longitudinal study, data from one patient are more likely to be similar to each other than other data from across the cohort. On a higher level, patients cluster within clinicians, who themselves cluster within hospitals. For example, treatment strategies may be more similar across clinicians from a single hospital than if compared with other clinicians nationwide.

Clustering of patient data may be reflected in the correlation of the residuals. A residual in a linear regression is the difference between the observed and modelled value for a particular data point [346], represented by $c$ in Equation 16. To be independent, residuals must not be autocorrelated [346]. That is, adjacent residuals must not be correlated with each other. To test for this, a scatterplot can be constructed with residuals on one axis and residual-1 on the other. A linear relationship indicates autocorrelation. This may be corrected by adding in a key omitted co-variate or transforming the variables [346]. Where data from the same patient may be autocorrelated in longitudinal modelling, covariate adjustment and random effects modelling may be undertaken.

Random effects modelling may be undertaken for linear, logistic or negative-binomial regression models. Adding a random effect introduces the assumption of 'exchangeability'. This means that each cluster should represent a random draw from a larger population of these clusters. For example, if patients were the cluster level, they could be randomly assigned cluster numbers and this would not result in a loss of information. However, if the clusters have a specific meaning, for example, ethnicities, or specific hospitals which may see more or less severe patients, cluster numbers could not be exchanged without losing some information. They are not 'exchangeable'. Therefore, the smaller the number of clusters, the less likely they are to be exchangeable. For small numbers of clusters, adjusting for the cluster as if it were a confounder is appropriate [347]. This introduces a 'fixed effect' into the model.

For each cluster in random effects modelling, the intercept alone or the intercept plus the slope of the group lines can be allowed to vary [348]. If varying the intercept only, the assumption is made that CYP may have different starting points, but that the gradient of

the association between the risk factor(s) and outcome of interest is the same [348]. Equation 16 describes this scenario whereby for person $i$ in cluster $j$, $Y$ is their outcome based on a magnitude $\beta$ of exposure $X$ plus the intercept $a$, error for first level which can vary (individual within cluster) $c$ and error for the cluster level $d$ which can also vary. This means that both $a$ and $\beta$ are the fixed terms, and both error terms $c$ and $d$ are the random terms. Since $\beta$ is a fixed term, it can be interpreted the same as for the basic linear model. In the paper exploring long-term outcomes following CID and MDA, CYP had multiple outcome measurements over time. To account for clustering by CYP, random effects were afforded by allowing random intercepts for data within each CYP.

$$y_{ij} = \alpha + \beta x_{ij} + c_{ij} + d_j \tag{16}$$

An alternative to adding random effects is to model the clustered data using cluster-robust models. These differ from multilevel modelling by correcting standard errors for clustering after implementing a regression model. These models assume a constant regression association across the specified clusters and therefore do not produce equivalent results to 'random slopes' multilevel modelling [348].

Assumption 2: There are no interactions between explanatory variables regarding the outcome

Interactions describe variables that, when considered together, associate with an outcome in a non-additive manner [349]. For example, in a given scenario, having an extra active joint may be associated with 0.50 points higher on the CHAQ. In addition, males may have 0.25 higher CHAQ scores than females. In this scenario we would expect a male with two active joints to have approximately 0.75 points higher on the CHAQ than a female with one active joint (Equation 17).

$$CHAQ = \alpha + 0.5 \cdot Active\ joints + 0.25 \cdot Gender + c \tag{17}$$

However, if the difference was 0.25 or 1.0, then gender may be modifying the effect of active joints on CHAQ score. This interaction can be incorporated into the regression equation (Equation 18).

$$CHAQ = \alpha + \beta_1 \cdot Active\ joints + \beta_2 \cdot Gender + \beta_3 \cdot Active\ joints \cdot Gender + c \tag{18}$$

Interactions can be tested between any covariates in a given model (Table 13). However, only those that are clinically plausible and relevant to the research question should be tested to avoid spurious results.

<u>Assumption 3: There is no collinearity between explanatory variables</u>

A third assumption of linear, logistic and negative-binomial regression models is that no pairs of variable in the model are collinear. Multicollinearity describes when two continuous variables are highly correlated. If both are included in a multivariable regression model, the effects of the variables are mixed, leading to increased estimates of the standard errors in addition to imprecise regression coefficient estimates [350].

Collinearity can be tested before constructing models through Pearson's correlations for normally distributed variables and Spearman's rank correlations for those that do not follow normal distributions (Table 13). Unlike Pearson's correlation, Spearman's rank correlation tests for the direction and strength of a monotonic (mutual increase or mutual decrease), rather than linear, relationship between two ranked variables. This test can incorporate non-normally distributed variables with outliers, which Pearson's correlation cannot [182]. For both correlation coefficients, a score of zero indicates no correlation with -1 and +1 equating to perfect negative and positive correlations (linear or monotonic relationships), respectively [182]. Specifically, correlation coefficient can be squared to give the percentage variation of x among y that is explained by both x and y. For example, a correlation coefficient of 0.9 between active and limited joint counts would give an $r^2$ value of 0.81. Thus, 81% of the variation in active joint count can be explained by the linear/monotonic relationship between active and limited joint counts.

If collinearity is indicated by a moderate or strong correlation coefficient, it may be appropriate to only include one of the collinear variables in the final regression model. This decision can be based on clinical relevance or statistically on the percent available data for each variable.

<u>Assumption 4: Linear associations between dependent and independent variables</u>

The fourth assumption of regression modelling applied differently to linear and negative-binomial versus logistic models. For continuous risk factors in linear regression models, the values of coefficients represent the increase in the outcome for every unit of the risk factor. For logistic and negative-binomial models, these represent an increase in the log(outcome) per unit of risk factor. Both of these types of associations require there to be a linear relationship between risk factors and some form of the outcome so that this coefficient remains constant for all values of the risk factor. This assumption can be tested graphically [341] (Table 13).

Assumptions 5 and 6: Model residuals are normally distributed and homoscedastic

The final two assumptions of regression models apply only to linear models and regard model residuals. These assumptions are that the residuals in linear models are normally distributed and homoscedastic. If residuals are not normally distributed, point estimates may still be unbiased [346]. However, tests of variance may be biased which may affect hypothesis testing and confidence in the point estimate. Normal distributions of variables and residuals can be tested graphically using histograms or quantile-quantile plots. In contrast, 'homoscedasticity' describes the constant variance of residuals across values of the regression line. If residuals are more deviant from the line for certain values, these are said to be 'heteroscedastic'. If this assumption is violated, point estimates should be unbiased [346]. However, coverage of 95% CIs may be biased and may therefore affect confidence and hypothesis testing. Homoscedasticity can be tested graphically by plotting the residuals against fitted values.

**Table 13.** Assumptions of linear, logistic and negative binomial regression models

| Model | Assumption | Testing the assumption |
|---|---|---|
| Linear Logistic Negative-binomial | The data are independently distributed | Scatterplot of residuals against residuals minus one. Clinically plausible associations |
| Linear Logistic Negative-binomial | There are no interactions between explanatory variables regarding the outcome | Addition of an interaction term into the model |
| Linear Logistic Negative-binomial | No pairs of variables are collinear | Pearson's or Spearman's correlation |
| Linear | Continuous risk factors and outcomes are linearly related | Scatterplot of individual risk factors against outcomes |
| Logistic Negative binomial | Continuous risk factors and log(outcomes) are linearly related | Scatterplot of individual risk factors against log(outcomes) |
| Linear | Residuals are normally distributed | Histogram or quantile-quantile plots |
| Linear | Residuals are homoscedastic | Scatterplot of residuals against fitted values |

### 4.3.3 Statistical Methods: How Common is Clinically Inactive Disease in a Prospective Cohort in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis? The Importance of Definition.

The aim of this paper was to quantify the achievement of CID and MDA at one year following initial presentation to paediatric rheumatology in the CAPS cohort. The proportions of CYP who had achieved CID according to Wallace's preliminary criteria, the JADAS and cJADAS were compared, as were the proportions of those having achieved MDA according to the JADAS, cJADAS or Magni-Manzoni criteria. The cohort was analysed as a whole and also within individual ILAR categories. If differences in the proportion defined as having achieved CID or MDA occurred between definitions, the reasons for this in terms of individual components were explored.

#### 4.3.3.1 Handling Missing Data

It was evident at an early stage in the analysis that the proportions of missing data in variables contributing to CID/MDA classification criteria were high. Therefore, a series of methods to handle these missing data were employed.

##### Complete Case Analysis

Unfortunately, due to the large volume of missing data within the components of particularly the JADAS and Wallace's preliminary criteria for CID, traditional complete case analysis would have only been possible in <5% of the cohort. As this traditional approach to complete case analyses would likely result in highly biased estimates in the few patients with complete data, a modified complete case analysis was performed. This approach was taken in order to more accurately estimate the proportion of patients in each CID/MDA state.

Patients with incomplete data that, based on values of recorded variables, could not have achieved CID, were classified as not in CID at one year. For example, those missing a PGA score but were known to have two active joints could not be in CID on any criteria, regardless of the value of missing data. This allowed the classification of a greater number of participants, but was expected to underestimate the proportion of patients in CID, since only those with incomplete data who could not have achieved the outcome could be classified.

##### Extreme Scenario Analysis

Before imputation methods were implemented, extreme scenario analyses were undertaken. This involved the classification of CYP with missing outcome data, which

hadn't been able to be classified under the modified complete case analysis, into CID/MDA according to each definition. The proportions of CYP fulfilling each CID/MDA definition were then estimated for the entire cohort. Following this 'best case' scenario, CYP with missing outcome data were then classified as not having fulfilled each CID/MDA criteria. A further 'worst case' estimation of the proportion of CYP having fulfilled each CID/MDA definition in the entire cohort was completed. These analyses determined whether there was any clinically meaningful difference in outcome achievement if missing outcome data were classified as 'not in CID/MDA' versus 'in CID/MDA'.

*Multiple Imputation under MNAR Assumptions*

At one year, where data to classify CYP in CID/MDA were missing, either all components were missing, for example where CYP had dropped out of the study, or a selection of components were missing with a selection available for analysis. Information regarding reasons for study attrition was available in most cases.

In total, eight reasons for missing data were defined (Table 14). In the majority of cases, it was clear that a MAR mechanism for the missing values was a clinically implausible assumption. This was due to a combination of exploration in CAPS data of previous disease activity in those with missing values and published evidence regarding disease activity in patients lost to follow-up compared to those retained in study populations [250,351]. These sources suggested that, in certain circumstances, patients with incomplete data or those lost to follow-up were more likely to be in CID than patients with available data [250,351]. Expert opinions from both paediatric rheumatology as well as adolescent/adult rheumatology specialists were then sought on the likely disease activity of patients in each of the eight missing data categories.

Different assumptions regarding each participant's disease activity were placed depending on which missing data group they belonged. The following groups of patients were presumed to have no active disease: those discharged 'well', those who repeatedly did not present to clinical appointments (presumed well) and those discharged to adult clinics (well at the point of transfer of care).

In some cases, where patients had been transferred to another clinic, it was unclear whether a CYP had been transferred to another paediatric clinic or to adult rheumatology. It was more likely that adolescents were transferred to adult rheumatology than younger patients. Using information from those known to have transitioned to adult care, it was

evident that in some cases, transition occurred years after a CYP's 16th birthday and in others, they were transferred as early as age 14, this indicating no consistent pattern of transition across the CAPS centres. Therefore, to maximise sensitivity for the assumptions, where the type of receiving clinic was unclear, patients were assumed to have transferred to adult rheumatology if over the age of 14.5 years old (Table 14). For those that had been discharged for other reasons, including moving house, missing data were assumed MAR, similar to those under the age of 14.5 years of age transferred to other clinics.

A seventh category of "lost-to-CAPS-follow-up" was defined. No data were available and it was unknown if the CYP had been formally discharged from the clinic. In these cases, the assumption was made that CYP had failed to attend clinical appointments and were treated in the same way as those discharged after failure to attend.

The assumptions placed on these first seven groups of patients were expected to marginally overestimate the proportion of CYP achieving CID/MDA. In addition, certain outcome definitions shared components, such as active joint counts which are a feature of every outcome definition. Assuming a similar lack of disease activity in these components would also, therefore, likely overestimate the overlap in groups of patients identified by the definitions. However, these assumptions were deemed more clinically appropriate than assuming missing data were MAR.

The final category of missing data corresponded to CYP who did attend clinical appointments but had partial data on the outcomes recorded. In these cases, as partial information was available, the majority of the data were inferred using multiple imputation assuming data were MAR. Multiple imputation comprised the creation and pooling of results in 20 imputed datasets. For all variables, imputation models included each component criteria at both initial presentation and one year, in addition to the age, gender and disease duration at initial presentation, ILAR subtype, hospital and the prescription of NSAIDs, steroids or csDMARDs within six months following initial presentation (yes/no for each class of drug). Continuous variables were transformed to normally distributed variables before imputation and then transformed back to their original distributions following imputation for further analyses. An exception was for acute phase reactant values, which were presumed to be missing as not clinically indicated for collection, and therefore normal (Table 14).

**Table 14.** Assumptions made regarding missing remission criteria

| Reason for missing data | Assumed missing data type with regard to remission status | Analytical decision |
|---|---|---|
| Discharged 'well' | MNAR | CYP achieved CID/MDA |
| Repeat non-attendance | MNAR | CYP achieved CID/MDA |
| Transferred to adult rheumatology | MNAR | CYP achieved CID/MDA |
| Transferred to another clinic and aged <14.5 years | MAR | Missing values imputed assuming data MAR. |
| Transferred to another clinic and aged ≥14.5 years | MNAR | CYP achieved CID/MDA |
| Other reason for discharge, including moving house | MAR | Missing values imputed assuming data MAR. |
| Lost to follow-up | MNAR | CYP achieved CID/MDA |
| Presented to clinical appointment but incomplete data | MNAR if acute-phase reactants MAR otherwise | Acute-phase reactants assumed normal. All other missing values imputed assuming data MAR. |

CYP: Child or young person, MAR: Missing at random, MNAR: Missing not at random

#### 4.3.3.2 Data Analysis

The cohort was initially described using descriptive statistics. Since continuous variables were not normally distributed, these patient and disease characteristics were described using medians and IQRs.

As binary outcomes, the proportions of participants achieving each outcome state were reported. In addition, the percentage overlap between CYP identified by multiple CID/MDA definitions was reported.

Finally, the median (IQR) differences in continuous variables and percentage difference in binary variables between CYP who did not belong to the overlap groups were reported.

### 4.3.4 Statistical Methods: Long-term Outcomes Following Achievement of Clinically Inactive Disease in Juvenile Idiopathic Arthritis: the Importance of Definition

The aim of this paper was to compare disease outcomes cross-sectionally at one year and in the long-term (1-5 years) between those who did and did not fulfil the various low disease activity definitions at one year. The outcomes studied were limited joint count, functional ability, HRQoL and pain.

#### 4.3.4.1 Applying Criteria for Clinically Inactive Disease and Minimal Disease Activity to CAPS data

This paper was broken down into two distinct analyses. Initially, outcomes were compared following the fulfilment or non-fulfilment of different CID definitions. Secondly, outcomes were compared after the achievement of CID, MDA or neither of these states. All CYP were therefore classified as to whether they had achieved CID at one year according to Wallace's preliminary criteria and/or the cJADAS. For the first analysis, CYP were then further grouped into four groups: i) CID according to both Wallace's preliminary criteria and cJADAS10, ii) CID with cJADAS10 but not Wallace's preliminary criteria, iii) CID with Wallace's preliminary criteria but not cJADAS and iv) No CID with either criteria.

For the second analysis, all CYP were classified as to whether they achieved MDA according to cJADAS score and then further divided into three groups: i) CID according to cJADAS , ii) MDA but not CID according to cJADAS and iii) active disease (i.e. not MDA or CID).

#### 4.3.4.2 Outcome Selection

For the first analysis, the following outcomes were selected: absence of limited joints (yes/no) (to represent joint damage), CHAQ score (to represent functional ability) and the CHQ psychosocial scale (to represent HRQoL). This last measure was treated as both a continuous variable and also a binary outcome (score ≤ or >30, representing scores within two standard deviations of population averages), to reflect a cut-off for poor HRQoL [352].

To avoid circular reasoning, outcomes which were included in one CID/MDA criteria set but not another in the same analysis were not selected. This was due to a potential bias favouring the definition including the outcome as a criterion. For example, the PGE (and the closely related pain score) [213,234,353] were not selected as outcomes in the analysis of CID, as PGE is a component of the cJADAS criteria but not Wallace's preliminary criteria.

It was therefore possible that CYP fulfilling the cJADAS CID criteria would have superior PGE scores in the long-term than those fulfilling Wallace's preliminary criteria for CID.

For the second analysis which compared CID versus MDA, in addition to the outcomes listed above, a fourth outcome, pain, was also included. For this comparison, circular reasoning was avoided as PGE (potentially driven by pain) is a component of both the CID and MDA definitions according to cJADAS.

### 4.3.4.3 Handling Missing Outcome Data

Missing CID and MDA criteria data were imputed as previously described. However, these imputation models were constructed separately for each outcome, with annual outcome data from baseline to five years included in each model. In addition, pain at initial presentation and one year was used to inform CHAQ. Limited joint counts and CHAQ scores also informed pain outcomes. CHQ scores were not imputed and only a complete case analysis was undertaken as there were likely factors that drive these HRQoL scores not captured as part of CAPS. This excluded CYP with no CHQ scores at one year for the cross-sectional analysis. However, the longitudinal models incorporated CYP with CHQ scores at any time point between one and five years.

### 4.3.4.4    Associations with Outcomes at One Year

The cross-sectional associations between CID/MDA state at one year and the outcomes at one year were assessed using multivariable regression models. The choice of model differed according to the outcome measure. Logistic regression was used for the two binary outcomes (absence of limited joints, CHQ psychosocial scores ≤30), linear regression was used for the CHQ psychosocial and pain scores and zero-inflated negative binomial regression was used for CHAQ, which is known to have a flooring effect where scores cluster around the lower (better) end of the scale [212]. Each model was also adjusted for the following additional potential confounders, selected based on clinical relevance: hospital, gender, ILAR category, age and symptom duration at initial presentation in addition to the value of the respective outcome at initial presentation. Assumptions of the models were tested.

### 4.3.4.5 Associations with Longitudinal Outcomes

Longitudinal analyses assessed whether CID/MDA disease states at one year were associated with the selected outcomes over the longer-term, in this case out to 5 years. Similar regression models were used as described in the cross-sectional analyses. It was also necessary to account for within-person repeated measures. CAPS patients are

clustered within seven hospitals distributed across the country. Since there are few hospitals, this variable was adjusted for in multivariable analyses. The assumption of exchangeability, however, is more likely to be met for a large number of patients within the study population. Therefore, each patient was used as an individual cluster in multilevel longitudinal models. However, when modelling long-term functional ability as a function of CID/MDA state, robust clusters were used as an alternative to multilevel modelling and associations were assumed to remain constant across clusters. Random intercept models have not yet been developed in STATA with zero-inflated models in imputed data. Therefore, this approach was not taken in this case.

### 4.3.5 Statistical Analysis: Factors Associated with Remission in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis: the Importance of Definition

The final paper in this thesis looked to identify independent factors associated with remission between one and three years.

#### 4.3.5.1 Applying Criteria for Remission to CAPS data

For each time point from one to three years, CYP were classified as to whether they had fulfilled the CID for Wallace's preliminary criteria (yes/no) and for the cJADAS10 (yes/no). A period of remission requires the maintenance of CID over a period of time. Under Wallace's preliminary criteria, this is six months for CRM and one year for CR. The shortest time windows available in CAPS data are annual. Therefore, two consecutive annual follow-up points in CID were considered for remission for each definition. Since medication may not have coincided with the annual follow-up points, this factor was not considered as part of the remission criteria.

#### 4.3.5.2 Handling Missing Data

Components of the CID definitions at each annual follow-up out to year three were imputed over 20 datasets under the MNAR and MAR assumptions as previously detailed. Imputation models included all potential predictors, except for IMD, which was only available for participants living in England. Missing data for this variable were not imputed due to the likely unmeasured factors that would inform their values. Therefore a separate imputation model was constructed in a subset of patients with complete IMD scores.

### *4.3.5.3 Investigating Independent Associations with Remission*

*Selection of Variables for Inclusion in Multivariable Models*

The variable pool was selected through i) Clinical plausibility, ii) Collinearity with other variables and iii) The volume and type of missing data within each variable.

Clinical plausibility was based on existing evidence on this topic in addition to discussions with rheumatologists. Collinearity between variables was assessed via Spearman's correlations. In addition, where missing data existed which could not be reasonably imputed due to unknown or unmeasured drivers of these data, variables were excluded from the pool.

Demographic factors selected for the pool included age and disease duration at initial presentation to paediatric rheumatology, gender, ethnicity and socioeconomic status measured using the English IMD. Disease-related factors included active and limited joint counts, PGA and ESR at both initial presentation and their change over the first year. Patient-reported factors included CHAQ score, PGE and pain score.

Initially, the associations between each potential predictor and the outcome were tested using univariable models. Subsequently, multivariable models were constructed. All models were built using simultaneous entry selection procedures based on clinical plausibility, with no further variable selection procedure applied. Collinearity of included variables was assessed. No interaction terms were tested due to a lack of clinically plausibility.

# Chapter 5

# The CAPS Cohort

*This chapter describes the CAPS cohort. Each paper included in this thesis used different inclusion dates based on the requirement of individual analyses. Therefore, for the purpose of illustration, this chapter will present the details of CYP recruited to CAPS up to 31st December 2013, the cut-point of the second results chapter. It includes information regarding missing data as well as attrition over the study follow-up period. These data give an overview of the population of CYP within CAPS and will inform the analyses presented in the subsequent results papers.*

# 5 THE CAPS COHORT

## 5.1 Introduction

This chapter summarises the characteristics of the CAPS cohort recruited up to 31$^{st}$ December 2013, including demographic features, disease features and patient reported factors in addition to broad medications prescribed. Further, quantities and reasons for various missing data within the cohort are summarised, with participant characteristics compared across different reasons for missingness. Across the majority of data presented in this chapter, the results are presented for the entire cohort and then limited to those with (a) ILAR oligoarthritis and (b) ILAR polyarthritis RF-negative and positive combined.

## 5.2 Patient Recruitment

Between January 2001 and December 2013, 1510 participants had ever been recruited to CAPS from seven rheumatology centres. Thirty two had been 'recruited' but no study forms were ever returned. As such, no further information regarding these participants was available and they were therefore excluded from all analyses. Of the remaining participants, the overwhelming majority had a physician's diagnosis of JIA. However, 60 had a diagnosis other than JIA and were excluded from all analyses.

All but three CYP were incident cases of JIA. Three CYP had been prescribed a biologic therapy prior to initial presentation at another paediatric rheumatology centre not participating in CAPS. Therefore, for the purpose of this thesis, these CYP were defined as prevalent cases and excluded from all further analyses. This left 1415 CYP with JIA recruited to December 2013.

## 5.3 Demographic Features

The majority of participants were female (65%) and of white ethnicity (90%). Although the median age at symptom onset was 7 years (IQR 3 to 11), the distribution was bimodal, with approximate peaks at two and 12 years. These peaks differed between ILAR categories, with later ages at both onset and presentation to paediatric rheumatology for patients with polyarthritis, particularly where RF-positive (Table 15, Figure 10).

**Table 15.** Demographic features of the CAPS cohort, shown for the entire cohort and within subsets limited to oligoarthritis (ILAR oligoarthritis persistent and extended only) and polyarthritis (ILAR RF- polyarthritis and RF+ polyarthritis only)

| Demographic factor | % available | Entire cohort | Oligoarthritis only | Polyarthritis only |
|---|---|---|---|---|
| | | Median (IQR) or N (%) | | |
| n | | 1415 | 707 | 341 |
| Age at onset (years) | 99 | 6.6 (2.7, 10.9) | 5.3 (2.3, 9.8) | 6.7 (2.7, 10.6) |
| Age at initial presentation to paediatric rheumatology (years) | 100 | 7.7 (3.5, 12.0) | 6.5 (3.0, 11.0) | 8.2 (3.6, 11.6) |
| Symptom duration to initial presentation (months) | 98 | 5.4 (2.8, 11.5) | 5.5 (2.9, 11.5) | 5.7 (3.3, 12.0) |
| Female | 100 | 917 (65) | 469 (66) | 266 (78) |
| White ethnicity | 98 | 1238 (90) | 622 (90) | 304 (91) |
| **Enrolling centre (Year joined study):** | 100 | | | |
| Alder Hey Children's Hospital, Liverpool (2001) | | 559 (40) | 293 (41) | 119 (35) |
| Royal Manchester Children's Hospital, Manchester (2001) | | 278 (20) | 151 (21) | 56 (16) |
| Great North Children's Hospital, Newcastle (2003) | | 122 (9) | 70 (10) | 31 (9) |
| The Royal Hospital for Children, Glasgow (2003) | | 170 (12) | 70 (10) | 54 (16) |
| Great Ormond Street Hospital, London (2006) | | 235 (17) | 105 (15) | 71 (21) |
| The Royal Hospital for Sick Children, Edinburgh (2011) | | 45 (3) | 16 (2) | 9 (3) |
| University College Hospital, London (2013) | | 6 (<1) | 2 (<1) | 1 (<1) |

IQR: Interquartile range
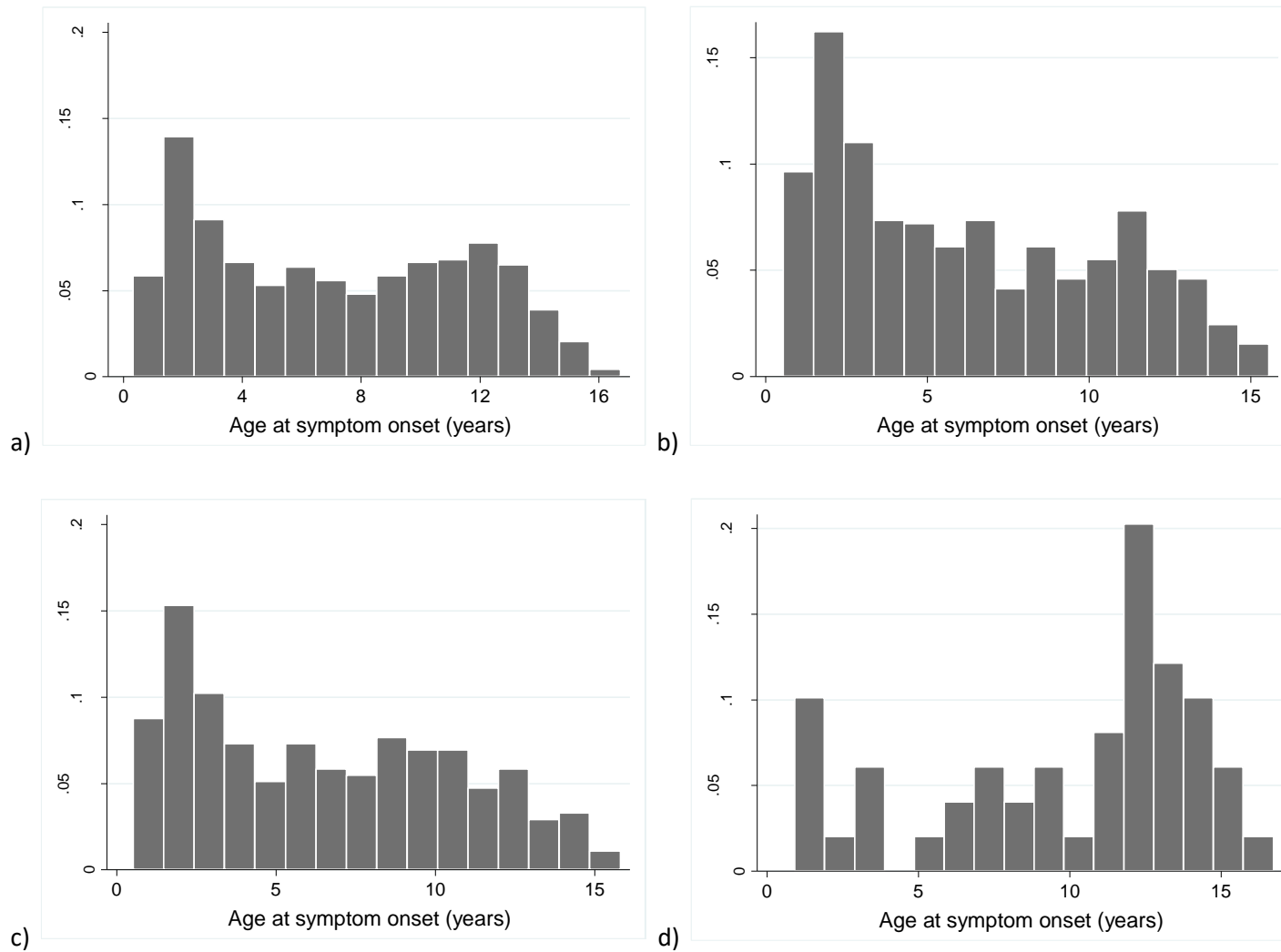
**Figure 10.** The distribution of ages at initial presentation to paediatric rheumatology in patients recruited to CAPS in a) the entire cohort, b) oligoarthritis only, c) RF-negative polyarthritis only and d) RF-positive polyarthritis only

## 5.4 Disease Characteristics

The most common ILAR category classified within the first year of disease in the CAPS cohort was oligoarthritis (50%), followed by RF-negative polyarthritis (21%). The least common category was RF-positive polyarthritis (4%). CYP with polyarticular JIA experienced consistently higher levels of disease activity than those with oligoarthritis. Distributions of disease activity parameters at initial presentation were heavily right skewed with greater levels of lower disease activity (Figure 11 a & b, Table 16).

**Table 16.** Disease characteristics of the CAPS cohort

| Disease factor | % available at initial presentation | Entire cohort | Oligoarthritis | Polyarthritis | % available at one year | Entire cohort | Oligoarthritis | Polyarthritis |
|---|---|---|---|---|---|---|---|---|
| | | **Initial presentation** | | | | **One year** | | |
| | | Median (IQR) or N (%) | | | | Median (IQR) or N (%) | | |
| **ILAR category:** | | | | | | | | |
| Systemic | | 96 (7) | | | | | | |
| Oligoarthritis | | 707 (50) | | | | | | |
| RF-negative polyarthritis | | 292 (21) | | | | | | |
| RF-positive polyarthritis | 100 | 49 (4) | | | | | | |
| Enthesitis-related | | 77 (5) | | | | | | |
| Psoriatic | | 97 (7) | | | | | | |
| Undifferentiated | | 97 (7) | | | | | | |
| Active joint count | 90 | 2 (1, 5) | 1 (1, 2) | 7 (4, 14) | 71 | 0 (0, 1) | 0 (0, 1) | 0 (0, 2) |
| Limited joint count | 90 | 1 (1, 3) | 1 (1, 2) | 5 (2, 10) | 71 | 0 (0, 1) | 0 (0, 1) | 1 (0, 2) |
| PGA (10cm VAS) | 66 | 2.9 (1.5, 5.0) | 2.2 (1.2, 3.8) | 4.4 (2.8, 6.4) | 58 | 0.5 (0.0, 1.8) | 0.3 (0.0, 1.5) | 0.7 (0.0, 1.9) |
| ESR (mm/hr) | 63 | 21 (7, 49) | 14 (5, 28) | 30 (10, 60) | 19 | 8 (4, 19) | 8 (5, 20) | 8 (3, 16) |
| CRP (mg/L) | 60 | 7 (4, 27) | 5 (4, 9) | 14 (5, 44) | 17 | 4 (3, 7) | 4 (3, 7) | 4 (4, 7) |
| Uveitis (acute or chronic) | 56* | 31 (4) | 16 (5) | 5 (3) | 53 | 57 (8) | 34 (10) | 10 (5) |
| Systemic features in systemic JIA | 98 (of systemic JIA) | 89 (95) | | | 73 | 39 (56) | | |

Total n=1415. *Further data upload following the publication of the initial study in this thesis meant that a greater volume of data regarding uveitis was available at the time of preparation of this chapter. CAPS: Childhood Arthritis Prospective Study ILAR: International League of Associations for Rheumatology, IQR: Interquartile range, RF: Rheumatoid factor, PGA: Physician global assessment, VAS: Visual analogue score, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, JIA: Juvenile idiopathic arthritis
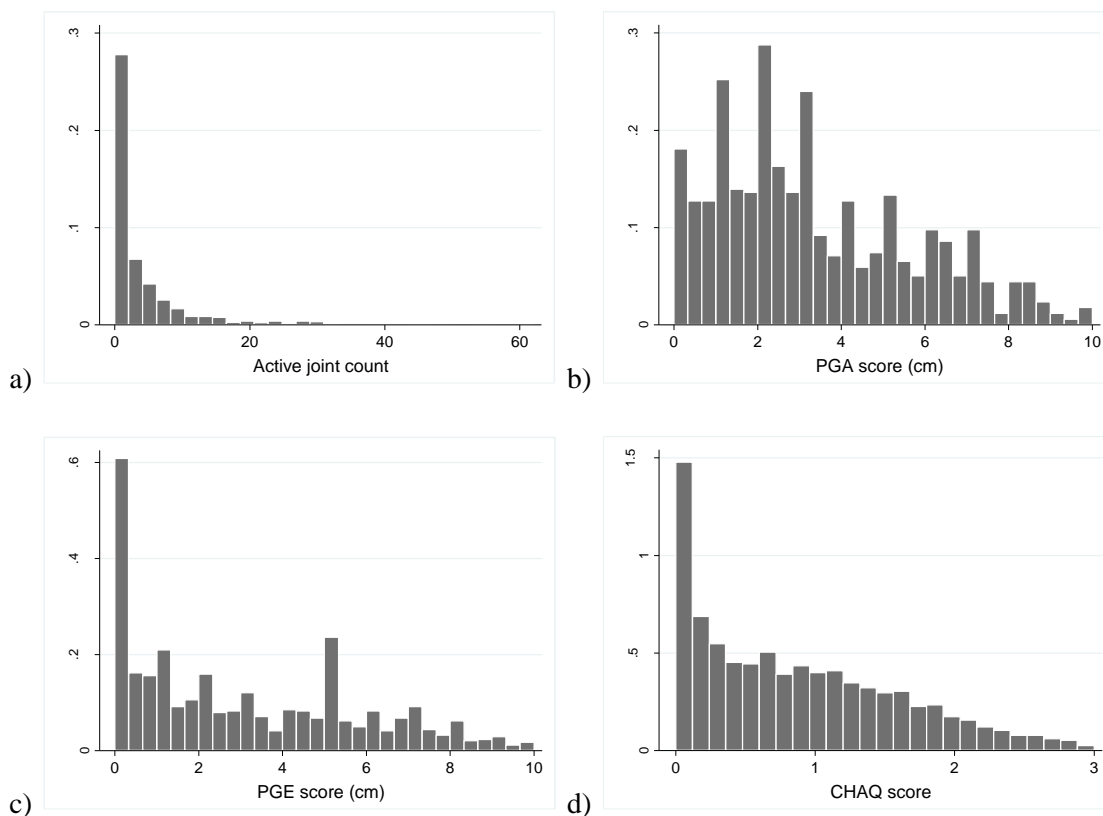
**Figure 11.** Distributions of active joint counts, PGA scores, PGE scores and CHAQ scores at initial presentation to paediatric rheumatology in the entire cohort

## 5.5 Patient-reported Outcomes

The median PGE score was 2.7cm (IQR 0.7cm to 5.6cm) and the median CHAQ score was 0.75 (IQR 0.13 to 1.38). PGE, CHAQ and pain were heavily right-skewed (Figure 11 c & d), with CYP with polyarthritis recording higher scores than those with oligoarthritis. In contrast, there were clinically similar CHQ psychosocial scores between the ILAR categories (Table 17).

**Table 17.** Patient-reported factors at initial presentation to paediatric rheumatology and one year in the CAPS cohort

| Patient-reported factor | % available at initial presentation | Initial presentation | | | % available at one year | One year | | |
|---|---|---|---|---|---|---|---|---|
| | | Entire cohort | Oligoarthritis | Polyarthritis | | Entire cohort | Oligoarthritis | Polyarthritis |
| | | Median (IQR) | | | | Median (IQR) | | |
| PGE (10cm VAS) | 66 | 2.3 (0.5, 5.0) | 1.7 (0.3, 4.9) | 3.5 (1.1, 5.7) | 66 | 0.6 (0.1, 2.9) | 0.4 (0.0, 2.2) | 1.1 (0.2, 3.6) |
| CHAQ score (range 0-3) | 69 | 0.8 (0.1, 1.4) | 0.6 (0.1, 1.1) | 1.3 (0.6, 1.8) | 66 | 0.3 (0.0, 0.9) | 0.1 (0.0, 0.8) | 0.4 (0.0, 1.1) |
| Pain (10cm VAS) | 66 | 3.0 (0.9, 5.8) | 2.3 (0.7, 5.0) | 4.6 (1.3, 7.0) | 66 | 1.0 (0.1, 3.6) | 0.7 (0.0, 3.2) | 1.2 (0.2, 4.0) |
| CHQ Psychosocial score (range 0-100) | 67% of those ≥8 years minimum age 32% of entire cohort | 50 (39, 56) | 51 (42, 57) | 47 (35, 54) | 54 | 52 (43, 58) | 53 (45, 59) | 51 (40, 57) |

For PGE, CHAQ and pain scores, higher scores indicate worsening wellbeing, function and pain, respectively. Higher scores on the CHQ indicate higher health-related quality of life.

CAPS: Childhood Arthritis Prospective Study, IQR: Interquartile range, VAS: Visual analogue score, CHAQ: Childhood Health Assessment Questionnaire, CHQ: Child Health Questionnaire

## 5.6 Exposure to Anti-rheumatic Therapies

Within the six months following initial presentation to paediatric rheumatology, 66% of the cohort had been prescribed steroids, 38% csDMARDs and 5% a biologic therapy. Of those prescribed steroids (n=940), 97% had data on the route of administration (n=915). Of these, in the first instance, 23% were administered orally, 6% intravenously and 70% via intraarticular injection, with a greater proportion of patients with oligoarthritis (84%) having had intraarticular injections compared with polyarthritis (60%). There were a higher number of csDMARD and biologic therapy prescriptions in patients with polyarthritis (csDMARD 70%, biologic 9%) compared with oligoarthritis (csDMARD 14%, biologic 1%) (Table 18).

**Table 18.** Medications prescribed within the first six months following initial presentation to paediatric rheumatology in the CAPS cohort

| Medication prescribed within six months following initial appointment | Entire cohort | Oligoarthritis | Polyarthritis |
| --- | --- | --- | --- |
| | | N(%) | |
| Steroids - any overall | 940 (66) | 481 (68) | 237 (70) |
| Oral administration | 213 (23) | 63 (13) | 63 (28) |
| Intraarticular administration | 640 (70) | 398 (84) | 134 (60) |
| Intravenous administration | 54 (6) | 15 (3) | 24 (11) |
| csDMARD | 544 (38) | 98 (14) | 240 (70) |
| Biologic | 69 (5) | 5 (1) | 30 (9) |

Routes of administration describe the first instance for drug class.

## 5.7 Missing Baseline and One Year Data

At initial presentation to paediatric rheumatology, missing data were evident for nearly all variables collected. Similar proportions of available data were evident across the majority of physician and patient-reported data items, at between 60 and 70%, respectively. However, greater availability was evident for joint counts and ILAR category. The largest volume of missing data were for acute phase reactants ESR (37% missing) and CRP (40% missing). In addition, a large proportion of data regarding uveitis activity was missing (44% at initial presentation) (Table 16 & Table 17). The reason for missing uveitis data is not known but may relate to the fact that the child may not yet have attended for ophthalmology screening and therefore the missing values indicate unknown.

At one year, completion of patient-reported questionnaires remained similar. However, lower availability of clinical items including both physician assessments and measures of inflammation, such as joint counts and acute-phase reactants, was evident. The greatest volume of missing data continued to be for acute-phase reactants, with 81% of ESR data and 83% of CRP data missing at on year.

## 5.8 Loss to Follow-up

### 5.8.1   Types of Loss to Follow-up

The attrition and missing data rates are presented for the first five years following initial presentation from December 2013 (Figure 12). At the time of analysis (2018), all CYP recruited to 2013 had been in the study for at least four years.

Flow and retention rates throughout the first 5 years of follow-up in CAPS are detailed in Figure 12, with missing data over key outcomes detailed in Figure 13. The most frequent reason for not attending clinical visits included in CAPS was discharge from paediatric rheumatology. The reasons for discharge were available in a majority of CYP who left the study (90%), with the most common reasons for discharge being a move to a different clinic (40% of all discharges over the first five years), 'well' (31% over the first five years), or recurrent failure to present to clinical appointments (22% over the first five years). Few patients were discharged for "other" reasons. However, no free-text was provided for additional clarification when patients were discharged for this reason. One CYP died over the course of study. Finally, a small number of CYP were lost-to-follow-up in CAPS (n=43). The reasons for these losses may be gained upon further contact with recruiting centres. However, these forms have not currently been returned.

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Total JA recruited to CAPS by December 2013: **1510**

Removed:
-60 not JIA
-32 no medical case notes
-3 not incident cases
(biologics<baseline)

Total JIA recruited to CAPS by December 2013: **1415**

**Baseline**

Lost to follow-up:
-76 discharged:
- 24 well
- 30 repeat DNA
- 22 moved clinic
- 9 lost to follow-up

Total at follow-up: **1330**

**Year 1**

Lost to follow-up:
-1 skipped this follow-up
-86 discharged:
- 31 well
- 14 repeat DNA
- 32 moved clinic
- 1 died
- 8 other
- 4 lost to follow-up

Total at follow-up: **1239**

**Year 2**

Lost to follow-up:
- 1 skipped this follow-up
93 discharged:
- 25 well
- 45 moved clinic
- 17 repeat DNA
- 6 other
- 2 lost to follow-up

Total at follow-up: **1143**

**Year 3**

Lost to follow-up:
-12 skipped this follow-up
-86 discharged:
- 19 well
- 17 repeat DNA
- 40 moved clinic
- 10 other
- 28 lost to follow-up

Total at follow-up: **1017**

**Year 4**

Lost to follow-up:
-108 not yet followed to five years
-60 discharged:
- 26 well
- 10 repeat DNA
- 23 moved clinic
- 1 other
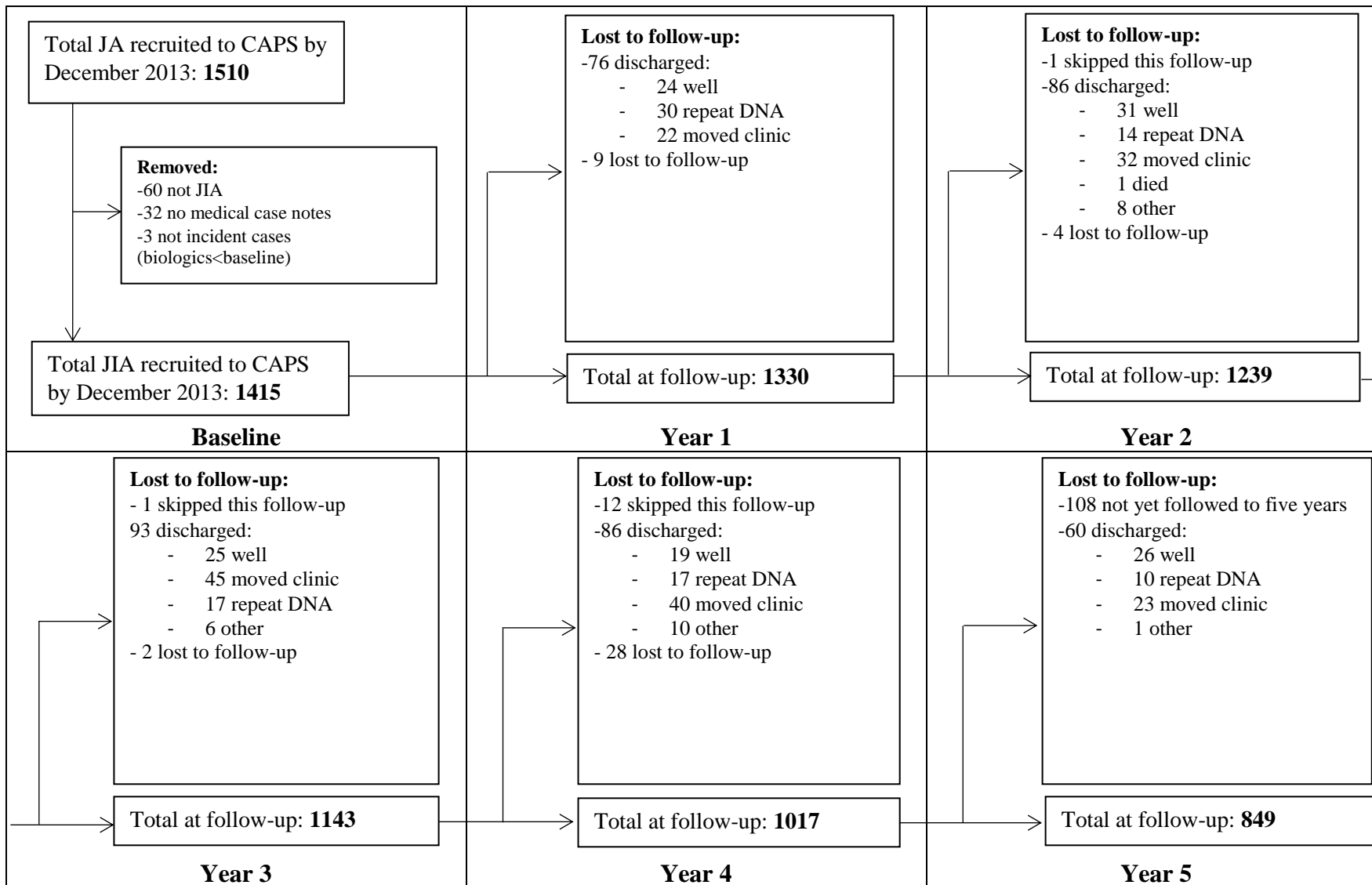
Total at follow-up: **849**

**Year 5**

**Figure 12.** Patient flow through CAPS for cohort recruited before December 2013, as used in section 6.2.
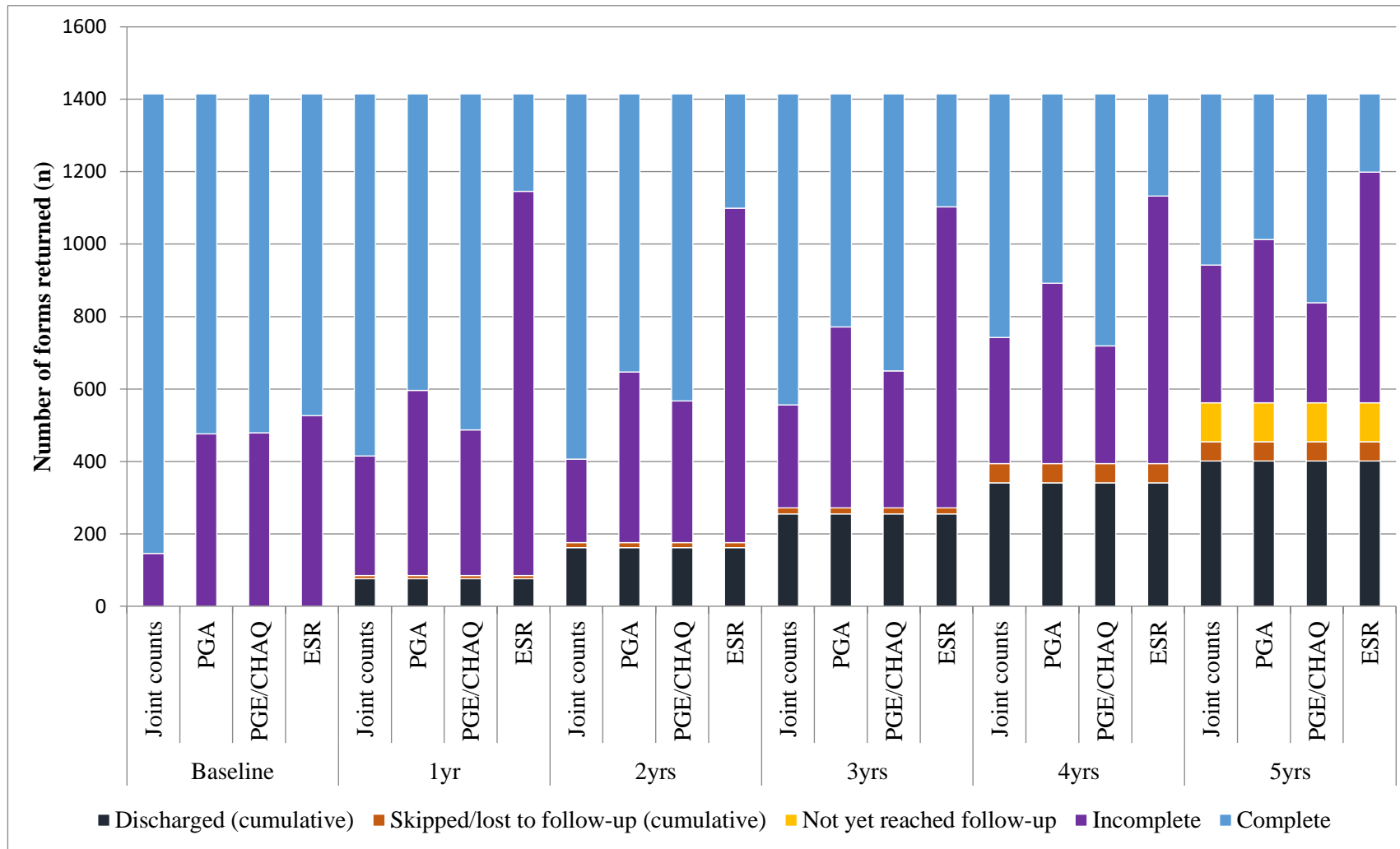
**Figure 13.** Number of forms returned at each follow-up for JIA core outcome variables. Pairs of variables that are completed on the same forms (active and limited joint counts, CHAQ and PGE) have been combined.

### 5.8.2 Differences in Baseline Characteristics Between Patients with Different Types of Loss to Follow-up

There were differences at initial presentation to paediatric rheumatology between patients who had remained in the study and those that had been ever discharged or lost to follow-up (Table 19). Those that had been discharged 'well' had the lowest baseline disease activity and patient-reported symptoms of all groups of patients analysed. These patients also had the lowest disease duration to initial presentation (median 4.1 months, IQR 1.9, 7.7), had greater representation of oligoarthritis (67%), lived in lesser deprived areas (24% in the 20% least deprived quintile) and were prescribed csDMARDs (17%) and biologic therapies (0%) infrequently. Similarly, CYP who repeatedly failed to present to clinical appointments had lower levels of disease activity, a higher proportion of oligoarthritis diagnoses (67%) and were less often prescribed steroids (50%), csDMARDs (13%) and biologics (0%) than those who remained in the study, similar to those who had been discharged 'well'. However, a greater proportion of patients who repeatedly failed to attend lived in areas of high deprivation (56% in the 20% most deprived areas) and patient-reported features were marginally higher than those who remained in the study, with median 3.4cm PGE scores (IQR 1.1, 5.0) compared with 2.9cm (IQR 0.7, 6.0) and 4.6cm pain scores (IQR 1.9, 5.5) compared with and 2.7cm (IQR 0.8, 5.5) at initial presentation, respectively (Table 19).

CYP who had moved to different clinics under the age of 14.5 years represented a similar cohort to those who remained in the study in terms of demographic features, except for a greater proportion being from more socioeconomically deprived areas (39% in the 20% most deprived areas compared with 25%, respectively). However, this group had a higher proportion of patients with oligoarthritis than those who remained in CAPS (68% versus 49%), a lower proportion of patients with RF-negative polyarthritis (12% versus 26%) and although they had similar disease activity parameters, function and pain, they had better wellbeing (PGE score 0.5cm (IQR 0.2, 3.8) versus 2.9cm (IQR 0.7, 6.0)) with fewer prescriptions for csDMARDs (18% versus 46%). In contrast, those who transferred to adult services or who transferred to an unknown clinic over the age of 14.5 years had different demographic, disease and patient-reported outcomes than those who remained in the study. These patients had an older age at initial presentation (median 14 years (IQR 13, 15) versus 6 years (IQR 3, 11)) and longer symptom durations to this time point (median 7 months (IQR 3, 15) versus 5 months (IQR 2, 9)). In addition, patients likely transferring to adult clinics had lower diagnoses of oligoarthritis than those who remained in the study (27% versus 49%), with greater diagnoses of all rarer ILAR categories. Although these

two groups of patients had similar disease activity, function and wellbeing, those that likely transferred to adult clinics experienced poorer pain scores (median 4.8cm (IQR 2.0, 7.2) versus 2.7cm (IQR 0.8, 5.5) and had higher prescription of biologic therapies (10% versus 6%) (Table 19).

Finally, those patients that were lost-to-follow-up in CAPS (n=43) were similar to those who repeatedly failed to attend clinical appointments in terms of the majority of demographic, disease and patient-reported features. However, this groups of CYP had lower representation of white ethnicity (67%), a higher proportion of patients with undifferentiated JIA (29%) and fewer prescriptions with steroids (43% lost to follow-up, 50% repeat non-attendance, 69% remained in CAPS (Table 19) than those who repeatedly failed to present to clinic appointments.

**Table 19.** Differences in demographic features, disease and patient-reported features between patients who remained and were lost-to-follow-up over the first 5 years from study registration

| Characteristic at initial presentation to paediatric rheumatology | Discharge reason within the first five years of follow-up | | | | | |
|---|---|---|---|---|---|---|
| | Remained in CAPS (n=849) | Discharged 'well' (n=125) | Moved clinic age <14.5 years (n=40) | Moved clinic age ≥14.5 years or note transferred to adult care (n=122) | Repeat non-attendance (n=88) | Lost to follow-up (n=43) |
| Duration in CAPS before discharge (years) | - | 2.8 (1.8, 4.1) | 2.0 (1.1, 2.7) | 3.3 (2.2, 4.1) | 2.9 (2.0, 4.1) | - |
| **Demographic features** | | | | | | |
| Age at initial presentation (years, median, IQR) | 6.2 (3.0, 10.5) | 7.8 (3.8, 11.7) | 7.6 (4.7, 10.2) | 13.9 (13.0, 14.9) | 10.6 (6.4, 12.5) | 9.6 (4.4, 12.8) |
| Disease duration to initial presentation (months, median, IQR) | 4.5 (2.2, 8.8) | 4.1 (1.9, 7.7) | 5.9 (3.4, 9.9) | 6.8 (3.4, 14.5) | 4.8 (2.4, 10.9) | 4.3 (1.3, 8.5) |
| Female (%) | 66 | 59 | 59 | 68 | 56 | 53 |
| White ethnicity (%) | 89 | 93 | 93 | 93 | 84 | 67 |
| *IMD (England only) (%):* | | | | | | |
| In 20% most deprived areas | 25 | 21 | 39 | 35 | 56 | 40 |
| In 60% middle IMD areas | 54 | 56 | 43 | 59 | 30 | 40 |
| In 20% least deprived areas | 21 | 24 | 17 | 7 | 14 | 20 |
| **Features of disease activity** | | | | | | |
| *ILAR category (%):* | | | | | | |
| Systemic | 7 | 6 | 10 | 9 | 3 | 6 |
| Oligoarthritis | 49 | 67 | 68 | 27 | 67 | 45 |
| RF-negative polyarthritis | 26 | 2 | 12 | 16 | 14 | 3 |
| RF-positive polyarthritis | 3 | 10 | 0 | 13 | 0 | 10 |
| Enthesitis-related | 3 | 4 | 7 | 17 | 6 | 0 |

| Characteristic at initial presentation to paediatric rheumatology | Discharge reason within the first five years of follow-up | | | | | |
|---|---|---|---|---|---|---|
| | Remained in CAPS (n=849) | Discharged 'well' (n=125) | Moved clinic age <14.5 years (n=40) | Moved clinic age ≥14.5 years or note transferred to adult care (n=122) | Repeat non-attendance (n=88) | Lost to follow-up (n=43) |
| Psoriatic | 7 | 7 | 0 | 15 | 6 | 10 |
| Undifferentiated | 5 | 4 | 2 | 4 | 4 | 29 |
| Active joint count (median, IQR) | 2 (1, 6) | 1 (1, 2) | 1 (1, 3) | 3 (1, 8) | 1 (1, 3) | 2 (1, 4) |
| Limited joint count (median, IQR) | 1 (1, 4) | 1 (0, 2) | 1 (1, 3) | 2 (1, 6) | 1 (0, 2) | 1 (1, 3) |
| PGA (cm, median, IQR) | 3.2 (1.9, 6.1) | 2.5 (1.5, 4.2) | 2.5 (1.6, 6.0) | 3.2 (1.8, 5.8) | 2.0 (1.0, 3.7) | 2.4 (0.8, 4.5) |
| ESR (mm/hr, median IQR) | 21 (8, 50) | 16 (5, 43) | 15 (6, 46) | 20 (8, 58) | 10 (4, 32) | 11 (3, 56) |
| **Patient-reported features** | | | | | | |
| CHAQ (median, IQR) | 0.8 (0.3, 1.4) | 0.3 (0.0, 1.1) | 0.4 (0.1, 1.4) | 0.9 (0.3, 1.5) | 0.9 (0.4, 1.4) | 0.4 (0.1, 1.4) |
| PGE (cm, median, IQR) | 2.9 (0.7, 6.0) | 1.6 (0.3, 4.5) | 0.5 (0.2, 3.8) | 3.2 (1.3, 5.0) | 3.4 (1.1, 5.0) | 3.2 (0.2, 7.0) |
| Pain (cm, median, IQR) | 2.7 (0.8, 5.5) | 1.7 (0.2, 4.8) | 2.0 (0.6, 4.1) | 4.8 (2.0, 7.2) | 4.6 (1.9, 5.5) | 3.0 (0.0, 6.2) |
| **Treatment in the first six months** | | | | | | |
| Steroid (any route) (%) | 69 | 68 | 63 | 66 | 50 | 43 |
| csDMARD (%) | 46 | 17 | 18 | 48 | 13 | 30 |
| Biologic (%) | 6 | 0 | 0 | 10 | 0 | 0 |

CAPS: Childhood Arthritis Prospective Study, IMD: Index of Multiple deprivation, IQR: Interquartile range, ILAR: International League of Associations for Rheumatology, RF:

Rheumatoid factor, PGA: Physician's global assessment, ESR: Erythrocyte sedimentation rate, CHAQ: Childhood Health Assessment Questionnaire, PGE: Parental global assessment,

csDMARD: Conventional synthetic disease-modifying anti-rheumatic drug.

# Chapter 6
# Results

*This results chapter combines four manuscripts which contribute to the journal format PhD. The first is a systematic review on the frequency of CID and remission in JIA. The second paper looks to see how well different definitions of CID capture the same group of children. The third looks at outcomes following achievement (or not) of CID at one year. The final paper looks at factors associated with remission.*

*The first three papers have been published and the citation included at the start of each paper. They are presented in their final published form, but to maintain the thesis style, are in formatted as a Word document rather than the journal print version, with section numbering added and references updated to sit consecutively with others in the thesis. The final paper is prepared for submission and formatted for The Annals of the Rheumatic Diseases.*

## 6.1 How Common is Remission in Juvenile Idiopathic Arthritis: A Systematic Review

Shoop-Worrall SJW, L Kearsley-Fleet, W Thomson, SMM Verstappen and KL Hyrich (2017). *How Common is Remission in Juvenile Idiopathic Arthritis: A Systematic Review*. Seminars in Arthritis and Rheumatism, 47(3): 331-337.

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**Word count (excluding references):** 2981

### 6.1.2 Abstract

**Objectives:** The ideal goal of treatment for juvenile idiopathic arthritis (JIA) is disease remission. However, many sets of remission criteria have been developed and no systematic review of remission in JIA exists.

The current systematic review investigated (1) how remission has been defined across JIA clinical cohorts, (2) the frequency of remission overall and within disease categories.

**Methods:** Studies using prospective inception cohorts published after 1972 were selected if they estimated remission in cohorts of ≥50 patients. Articles focusing on specific medical interventions, not defining remission clearly or not reporting disease duration at remission assessment were excluded. Studies were selected from Medline, Embase, PubMed and bibliographies of selected articles. Risks of selection, missing outcome data and outcome reporting biases were assessed.

**Results:** Within 17 studies reviewed, 88% had majority female participants and patient disease duration ranged from 0.5 to 17 years. Thirteen sets of criteria for clinically inactive disease and remission were identified. Uptake of Wallace's preliminary criteria was good in studies recruiting or following patients after their publication (78%).

Remission frequencies increased with longer disease duration from 7% within 1.5 years to 47% by 10 years following diagnosis. Patients with persistent oligoarticular and rheumatoid-factor positive polyarticular JIA were most and least likely to achieve remission, respectively.

**Conclusions:** Achievement of remission increased with longer disease duration, but many patients remain in active disease, even in contemporary cohorts. Multiple sets of outcome criteria limited comparability between studies.

**Key words:** Juvenile idiopathic arthritis, remission, clinically inactive disease, paediatric rheumatology, systematic review

**Abbreviations:** PGA: Physician's global assessment, PGE: Parental global assessment, ESR: Erythrocyte sedimentation rate, JADAS: Juvenile Arthritis Disease Activity Score, cJADAS: Clinical JADAS, PICO: Patient Intervention Comparison Outcome, JRA: Juvenile rheumatoid arthritis, JCA: Juvenile chronic arthritis, QA: Quality assessment, EULAR: European League Against Rheumatism, ACR: American College of Rheumatology, RF: Rheumatoid factor, ERA: Enthesitis-related arthritis, PsA: Psoriatic arthritis

### 6.1.3 Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood [354]. The presentations, treatments and outcomes are variable across this heterogeneous disease, but the main goal for all patients is disease remission, in order to prevent or reduce the long-term pathologies, such as pain and functional disability [4].

Various sets of remission criteria have been applied across clinical cohorts and in clinical trials, although most aim to identify a state of minimal or absent disease activity. Composite remission criteria often include one or more measures across the core JIA outcome variables including active joint counts, global assessment score of disease activity by physician's (PGA) or parents (PGE) and erythrocyte sedimentation rate (ESR) [161], with additional criteria including activity of systemic features for children and young people (CYP) with systemic JIA [165,185], presence of ocular inflammation in uveitis and length of morning stiffness [185]. The first validated composite criteria for assessing this disease state were Wallace's preliminary criteria for clinically inactive disease and remission in JIA (2004) [165], which divides remission into three distinct states: clinically inactive disease (i.e. no apparent disease activity at a single time point), remission on medication (i.e. clinically inactive disease maintained for at least six months whilst taking anti-rheumatic and/or anti-uveitis medication) and remission off medication (i.e. clinically inactive disease maintained for at least 12 months without medication) [165]. Other recent sets of criteria validated for use in JIA include cut-offs of the Juvenile Arthritis Disease Activity Score (JADAS) [168] and clinical JADAS (cJADAS) [186] to represent states of clinically inactive disease and remission.

The literature on the frequency of remission in JIA has never been reviewed systematically. Knowledge of the frequency of remission across clinical cohorts would provide an insight into the past and current disease course of JIA, both overall and within specific disease categories. Three narrative reviews [12,253,254] were published prior to, or in the immediate years after, the publication of Wallace's preliminary criteria [165]. Ravelli reported the frequency of remission in JIA at between 35% and 61% [254], with Adib and others estimating this frequency at between 33% and 56% [253]. In addition to pre-dating uptake of the validated sets of remission criteria for JIA, these reviews focused on cohorts largely recruited before the introduction of biologic therapies for JIA at the turn of the century [118]. Thus, the uptake of newer set of criteria for remission and the remission rates in cohorts with access to biologic therapies have not been described. In 2010, Shenoi and Wallace reviewed six studies that had utilised Wallace's preliminary criteria [355]. However,

studies reviewed were largely retrospective in design, therefore likely excluding a portion of CYP with milder disease features. The only prospective study reviewed was in CYP with systemic JIA, therefore the generalisability of the review to other recent JIA cohorts was limited. The review also did not consider how remission frequencies are affected with increasing disease duration.

The aims of this systematic review were therefore to: i) Investigate how remission has been defined across JIA clinical cohorts and ii) Describe the frequency of remission in cohorts of JIA overall and within individual disease categories.

### 6.1.4   Methods

#### 6.1.4.1     Search Strategy

Medline, Embase and PubMed databases were searched from January 1972 to March 2015 by author SJWS, using Patient Intervention Comparison Outcome (PICO) methodology to build the following strategy: P) Patients with juvenile rheumatoid arthritis (JRA) [8], juvenile chronic arthritis (JCA) [356] or JIA [1] I) No specified intervention C) Not applicable and dropped from search design O) Remission or clinically inactive disease. The study was built and reported according to PRISMA guidelines [357]. Patients of all ages and disease durations were included to summarise short and long-term remission frequencies. Synonyms of each PICO were applied (full search terms and hits detailed in Supplementary Table 1). Where articles were selected for inclusion, their bibliographies were also screened for further relevant papers.

#### 6.1.4.2     Inclusion and Exclusion Criteria

The inclusion criteria for studies included i) reported the frequency or proportion of patients in remission ii) utilised patients from inception cohorts with at least partial prospective data collection iii) were available in English iv) included at least 50 patients v) did not focus on remission following a specific medical intervention vi) did not recruit a specific group of patients based on investigations (e.g. imaging) or location of affected joints vii) included information on disease duration at time of remission assessment. Studies using the same patient population were included if reporting outcomes at different follow-up intervals or used different sets of outcome criteria.

Case reports, clinical trials and non-original research articles were excluded. Article titles and abstracts were independently reviewed by two reviewers SJWS and LKF, after which an agreed list of full text articles were screened independently. Full texts were accessed where abstracts suggested the study might meet the inclusion criteria or did not contain

enough information to assess relevance. Where studies from the same population reported the same outcome over the same follow-up period, the publication with the most detailed information on remission (e.g. used secondary criteria or time point) was selected and the other(s) excluded (n=2, [358,359]). Where there was disagreement or uncertainty at any stage, a third reviewer KLH adjudicated.

### 6.1.4.3 Quality Assessment

Risk of bias within selected articles was assessed using a modified version of Pasma et al. quality assessment (QA) tool [360] (Supplementary Table 2). 'Essential questions' assessed risk of bias associated with patient sampling method, disclosure of differences between consents and refusals, missing outcome data and outcome definition reporting. Non-relevant questions from the Pasma tool were dropped. In addition, a question on missing data bias, adapted from the Cochrane Collaboration tool for assessing risk of bias [361], was added.

For each of eight bias categories, one point was scored where evidence of avoiding or controlling for the relevant bias was evident. Articles that scored at least three out of the four on the 'essential' questions and at least five out of the eight in total were considered to be of high quality. Since studies were observational in design and did not focus on specific medical interventions, risk of bias across, rather than within, studies was not assessed.

### 6.1.4.4 Description and Evidence Synthesis

Information on study location, follow-up period, outcome sets of criteria and the frequency of remission were extracted independently. In addition, participant sampling frames were extracted.

Sets of criteria for clinically inactive disease or remission were identified and classified as 'validated' or 'investigator-defined'. If validated sets of criteria had been altered, this was noted but classed as 'investigator-defined'. For the purposes of the review, outcomes were classed as 'clinically inactive disease', where no evidence of disease activity was apparent at a single time point, or 'remission', whereby clinically inactive disease had been maintained off medication and/or for a specific length of time at assessment.

Estimates were compared between studies that assessed 'current-remission' at the end of follow-up. Additionally, estimates were compared between those assessing 'ever remission' throughout follow-up. Both clinically inactive disease and remission estimates were then compared between validated and investigator-defined sets of criteria and with

increasing disease duration. Finally, the ranges of clinically inactive disease and remission estimates across different ILAR categories were synthesised.

### 6.1.5 Results

Of 2427 unique articles identified, 17 were selected for inclusion to the systematic review (Figure 14). Of included studies, 16 reported the frequency of remission for the cohort overall and 11 for specific disease categories (Figure 14). Disease categories classified under European League against Rheumatism (EULAR) [356] or American College of Rheumatology (ACR) [8] EULAR or ACR criteria were pooled with corresponding categories in the ILAR criteria [1] (e.g. pauciarticular juvenile arthritis and oligoarticular JIA).

#### 6.1.5.1 Risk of Bias in Selected Articles

Overall, study quality was moderate with only 9/17 (53%) articles fulfilling the criteria for 'high quality' on the QA tool (Supplementary Table 2). Of the four key components, 15/17 (88%) reduced the risk of selection bias through appropriate sampling methods but only 11/17 (65%) reduced this risk through comparisons of patients consenting and not consenting to participate. In addition, 16/17 (94%) applied reproducible remission criteria. However, only 3/17 (18%) reduced the risk of missing data bias through not having missing outcome data or applying appropriate methodologies to manage these (Supplementary Table 3).

#### 6.1.5.2 Study Characteristics

The majority of patient populations were located in Europe (n=12, 71%) (Table 20). Cohorts were reasonably large, with the majority recruiting patients from multiple clinics (n=13, 76%) and only 3/17 (18%) following fewer than 100 patients. The most recent classification system (ILAR) was used in most studies (n=10, 59%), although of the remaining seven, four were published prior to the publication of this set of criteria (Table 20).

In the majority of patient populations, there were greater numbers of females than males (n=15). Oligoarticular JIA was frequently the most common disease category (n=14, 82%) and ranged from 17% [362] to 73% [268] of cohorts across all studies. Two popoulations from Taiwan comprised greater males than females, with enthesitis-related JIA the most common ILAR category [30,362] (Table 20).
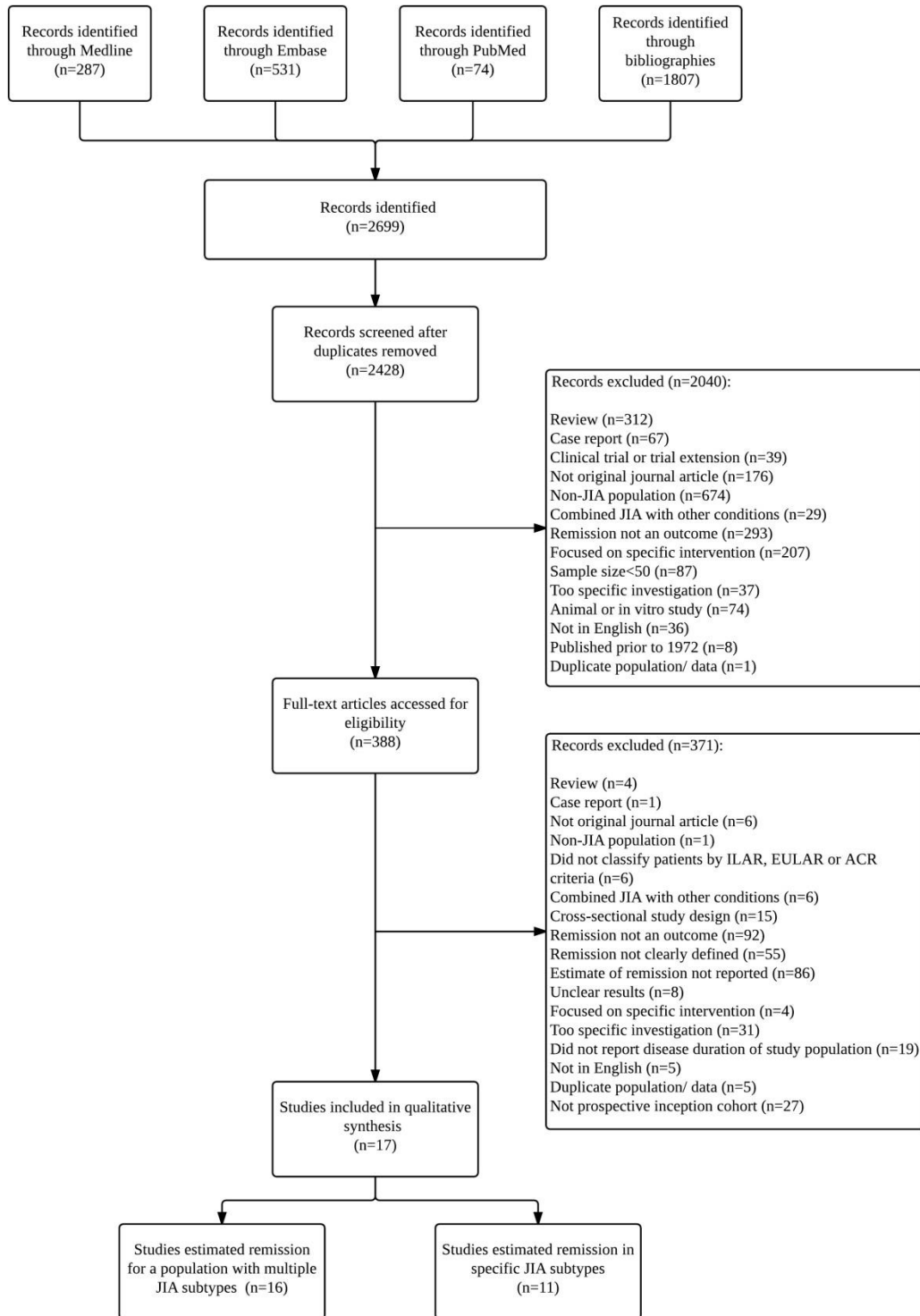
**Figure 14.** Number of articles accessed and reviewed to explore the frequency of remission in JIA. 'Too specific investigation' refers to inclusion criterion 6 in the text.

**Table 20.** Demographic and disease information of articles reviewed

| Author | Country | Sample size | Juvenile arthritis classific-ation | Percent female (%) | Percent by category (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Systemic | Oligo | RF- Poly | RF+ Poly | Total Poly | ERA | PsA | Undiff. |
| Multi-centre | | | | | | | | | | | | |
| Guzman et al., 2014 [5] | Canada | 1104 | ILAR | 64 | 7 | 38 | 21 | 4 | - | 14 | 6 | 10 |
| Berntson et al., 2014 [280] | From the Nordic JIA database | 192 | ILAR | 69 | 5 | 51 | 21 | 1 | - | 8 | 1 | 15 |
| Berntson et al., 2013 [276] | Scandinavia and Finland | 410 | ILAR | 66 | 4 | 47 | 18 | 1 | - | 11 | 3 | 15 |
| Shen et al., 2013 [30] | Taiwan | 195 | ILAR | 45 | 19 | 23 | 12 | 5 | - | 37 | 2 | 3 |
| Bertilsson et al., 2013 [257] | Sweden | 132 | EULAR | 64 | 7 | 64 | - | - | 22 | 5 | 2 | 0 |
| Shen et al., 2013 [362] | Taiwan | 58 | ILAR | 41.4 | 16 | 17 | - | - | 28 | 40 | - | - |
| Bertilsson et al., 2012 [363] | Sweden | 128 | EULAR | 64 | 4.7 | 64 | - | - | 27 | 3.1 | 1.6 | - |
| Nordal et al., 2011 [275] | Scandinavia and Finland | 440 | ILAR | 66 | 4 | 51 | 21 | 1 | - | 8 | 1 | 14 |
| Oen et al., 2009 [273] | Canada | 356 | ILAR | 66 | 7 | 41 | 20 | 4 | - | 10 | 7 | 12 |
| Berntson et al., 2007 [364] | Denmark, Norway, Sweden and Finland | 312 | ILAR | 72 | | 55 | 25 | 1.9 | - | 3.8 | 2.2 | 12 |
| Gäre et al., 1995 [255] | Sweden | 124 | EULAR | 65 | 3.2 | 58 | - | - | 29 | 4.8 | 4.8 | - |
| Gäre et al., 1995 [365] | Sweden | 124 | EULAR | 65 | 3.2 | 58 | - | - | 29 | 4.8 | 4.8 | - |
| Gäre et al., 1993 [366] | Sweden | Two groups: G1: 121 G2: 125 | EULAR | 65 (G1) 64 (G2) | 2 (G1) 4 (G2) | 31 (G1) 46 (G2) | | | 48 (G1) 40 (G2) | 15 (G1) 5 (G2) | 5 (G1) 5 (G2) | - |
| Single-centre | | | | | | | | | | | | |
| Padeh et al., 2013 [367] | Israel | 75 | ILAR | 65 | 8 | 68 | 11 | - | - | 4 | 4 | 5 |
| Selvaag et al., 2006 [368] | Norway | 197 | ACR | 61 | 7 | 56 | 28 | 3 | - | 4 | 3 | - |
| Kotaniemi et al., 2002 [268] | Finland | 372 | ILAR | 66 | - | 73 | 27 | - | - | - | - | - |
| Flatø et al., 1998 [369] | Norway | 72 | ACR | 54 | 6 | 44 | - | - | 24 | 17 | 10 | - |

Studies are listed first by whether cohorts are multi/single centre, by year of publication and finally according to sample size. Disease categories: Oligo: Oligoarticular, Poly: Polyarticular, RF: Rheumatoid factor, Total Poly: Polyarticular where RF status was not determined, ERA: Enthesitis-related, PsA: Psoriatic, Undiff.: Undifferentiated JIA, ILAR: International League of Associations for Rheumatology, EULAR: European League Against Rheumatism, ACR: American College of Rheumatology

### 6.1.5.3 The Frequency of Remission in Selected Studies

*Sets of criteria for clinically inactive disease and remission used*

Across 17 studies, 13 different sets of criteria for remission or clinically inactive disease were identified. The majority of these were investigator-defined. Only seven studies applied previously validated sets of criteria for remission in JIA in full: all applied Wallace's Preliminary Criteria (Supplementary Table 4).

*Point Prevalence Estimates using Wallace's preliminary criteria*

Of studies quantifying current clinically inactive disease and remission across the entire cohorts, seven of nine (78%) that followed at least part of their patient cohorts after their publication used Wallace's preliminary criteria.

The prevalence of current clinically inactive disease using Wallace's preliminary criteria increased between 33% [273] at six months to 67% [280] at eight years (Figure 15.a). Similarly, the prevalence of current remission off medication using Wallace's preliminary criteria increased from 7% at mean 1.5 years (±0.5 years) [367] to 42% at median eight years (IQR 7 to 12 years) [275] (Figure 15.b). Only two studies applied the criteria for remission on medication. At 9% and 15% after approximately 8 years of disease (IQR 6 to 13 years), these estimates were substantially lower than the estimates of remission off medication after similar follow-up [30,275] (Figure 15.b; Supplementary Table 4).

*Point Prevalence Estimates using Investigator-defined Sets of Remission Criteria*

Across cohorts, the prevalence of clinically inactive disease using investigator-defined sets of criteria varied widely between 19% [257] and 60% [369]. These estimates did not seem to be associated with disease duration (Figure 15.a). However, definitions of clinically inactive disease and remission were not always nested and many studies did not include CYP who were in remission into the estimates of clinically inactive disease [255,257,275,363,366]. There appeared to be a slight increase in remission achievement, using investigator-defined sets of criteria, over time from 26% [368] to between 40% and 50% [257,369] over a period of at least ten years of disease (Figure 15.b).
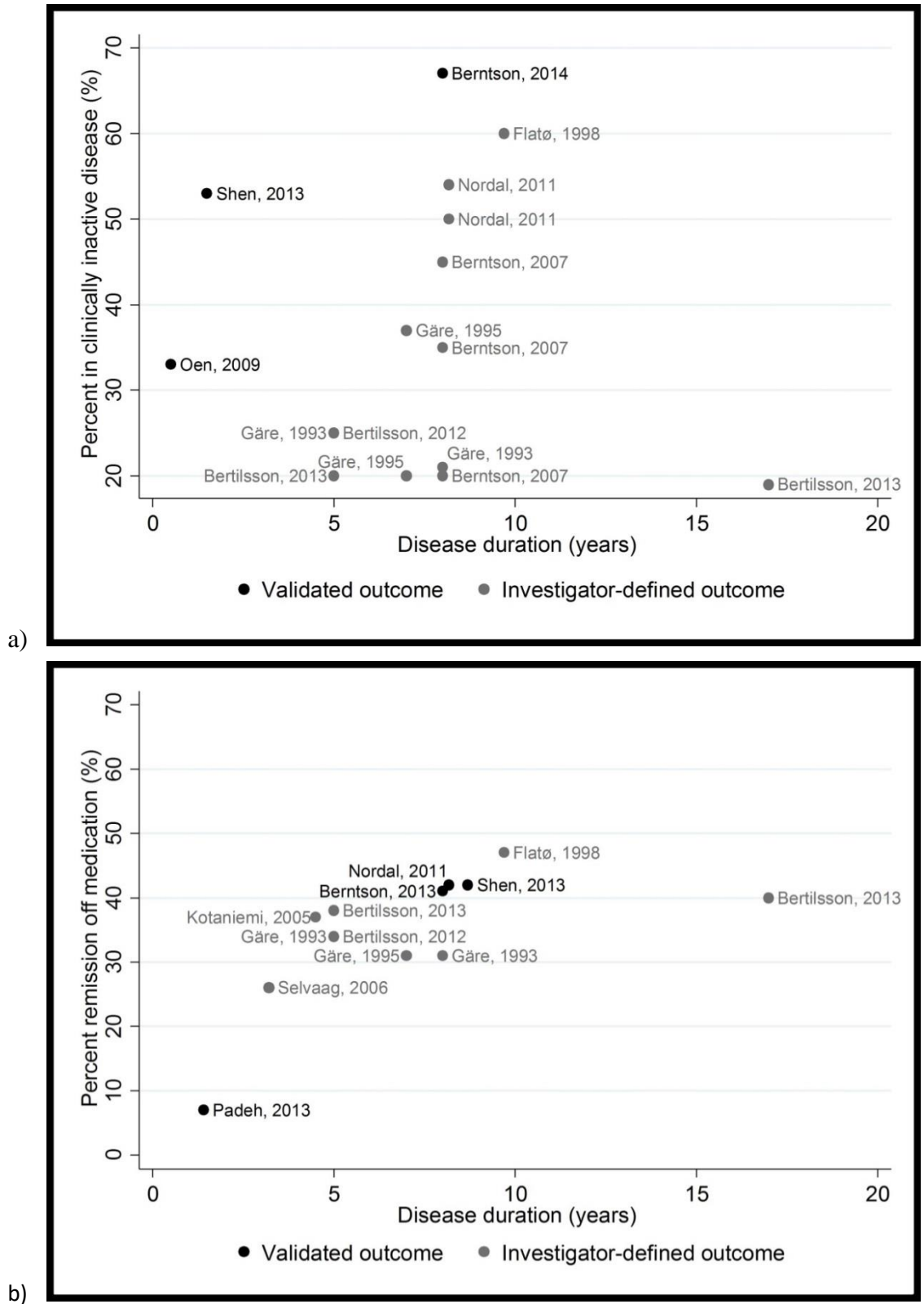
**Figure 15.** Percentage of patients with JIA in current a) clinically inactive disease or b) remission off medication across the literature. Point estimates are stratified based on whether outcome definitions were validated or investigator-defined. Where studies are listed multiple times, multiple sets of outcome criteria have been utilised (see Supplementary Table 4).

*Point Prevalence Estimates of Current Remission across ILAR categories*

Patients with persistent oligoarticular JIA appeared to achieve clinically inactive disease and remission most frequently when compared to other categories, with remission off medication estimates ranging from 39% at mean three years (±0.4 years) [368] to 66% at median nine years (IQR 6 to 13 years) [30]. In contrast, patients with RF-positive polyarticular disease and enthesitis-related JIA appeared to achieve these states the least often, with 2/5 studies on the former and 3/8 studies on the latter reporting that none of these patients achieved remission at follow-up [257,275,363,368]. Estimates from patients with systemic disease exhibited the largest variation, ranging from 0% [369] to 100% [255] in some form of clinically inactive disease or remission (Supplementary Table 4).

*Estimates of Ever Having Achieved Clinically Inactive Disease and Remission*

Only three studies investigated the cumulative percent of ever achieving clinically inactive disease or ever achieving remission over time [5,30,369]. Guzman et al estimated the ever achievement of clinically inactive disease to range from 45% within one year to 95% within five years. The estimates for ever remission off medication from this paper ranged from 4% within two years to 41% within five years following diagnosis with other estimates from longer follow-ups at 45% within median nine years (IQR 6 to 13 years) [30] and 81% within mean 10 years (±2 years) [369]. Guzman et al reported that patients with oligoarticular JIA achieved highest achievement and RF-positive polyarticular JIA the lowest achievement of remission, with 0% of this latter category ever achieving remission off medication within the first five years of disease [5].

### 6.1.6   Discussion

This systematic review aimed to quantify the frequency of clinically inactive disease and remission in patients with juvenile-onset arthritis. Patient populations spanned four continents, although the majority of the included studies originated in Scandinavia. The achievement of remission increased with increasing disease duration, although after over a decade of disease, fewer than half of patients have achieved this state. Large variations were identified in outcome criteria and resulting outcome frequencies.

With 13 sets of criteria for either clinically inactive disease or remission applied in 17 studies, comparability between estimates was compromised. Seven studies used a published set of criteria: Wallace's preliminary criteria, which have undergone internal validation [370]. It is likely that, particularly for earlier cohorts, all necessary measures were not collected from cohort inception to enable the use of published sets of criteria such as

Wallace's preliminary criteria. In addition, since blood tests are not mandatory for all patients in real-world observational cohorts, investigators frequently did not have all outcome data, such as ESR, to apply the full validated set of criteria. This is illustrated in that a maximum of three components of Wallace's preliminary criteria were used in any of the investigator-defined outcomes. However, the frequent altering of validated sets of criteria in a non-uniform manner means both that validated sets of criteria are no longer being used and that remission rates cannot be directly compared or pooled to attain an average. A consensus on how to apply published sets of criteria should be reached in order to standardise outcome assessment across clinical cohorts.

Whilst clinically inactive disease estimates were extremely variable in studies using investigator-defined sets of outcome criteria, a clearer trend was evident in cohorts using Wallace's preliminary criteria ranging from 33% at six months [273] to 67% at eight years [280]. The variation in estimates from studies using investigator-defined criteria sets likely stems from a combination of different outcome definitions and the non-inclusion of patients in remission into clinically inactive disease estimates in many of the studies [255,257,275,363,366]. By not combining CYP who have achieved clinically inactive disease and remission in the former estimates, these studies underestimate the achievement of clinically inactive disease. Across all cohorts, a greater number of patients achieved remission with increasing disease duration. This trend likely reflects initial disease control for patients responsive to first-line therapies and differential delays to effective therapies in patients with refractory disease. These remission estimates ranged from under 7% [367] early in the disease course to between 40 and 50% after 10-20 years of disease [257,369]. However, these latter reports likely underestimate remission due to the lack of biologic therapies for these older cohorts and likely attrition of patients due to low disease activity earlier in the disease course.

The clearer trend in remission estimates compared with those for clinically inactive disease likely stems from more similar sets of outcome criteria and the relative ease of capturing data on the former, since clinically inactive disease is a transient state and may last for only a short period before relapse occurs [370]. Thus, short periods of clinically inactive disease may not coincide with a study visit. Indeed, in three of the studies reviewed by Shenoi and Wallace, patients achieved clinically inactive disease multiple times over the study periods [355], but may not have retained this disease state long enough to be classified as in remission. Future studies should therefore attempt to measure 'ever' clinically inactive disease and remission to capture the changing disease processes of JIA.

Estimates of remission on and off medication differed substantially, particularly when Wallace's preliminary criteria had been used. Whilst remission on medication is intended as an intermediate between clinically inactive disease and remission off medication [165], these estimates fell below those of remission off medication in the current review. Since there are currently no published guidelines on when and how to discontinue treatment in JIA once clinically inactive disease has been achieved [371], it is likely that different tapering strategies existed across patient populations. Remission on medication cannot be measured if medication is discontinued at, or shortly after, achievement of clinically inactive disease. It is likely, therefore, that remission on medication can be captured in CYP with more severe disease, who may receive longer-term medication, potentially to avoid relapse [372]. In accordance, Shen and others reported rates of remission on medication that exceeded that off medication only in the more severe RF+ polyarticular category [30]. An alternative definition strategy was demonstrated by Flatø and others [373], who altered remission on medication on Wallace's preliminary criteria [165] to allow the maintenance of ID on or off medications for six months. By removing the requirement to be off medication, their estimate of remission on medication exceeded that of remission off medication and likely was a more representative intermediate between the two states.

Similar to all three previous reviews [253,254,355], this review corroborated that patients with persistent oligoarticular disease seem to have the most favourable disease course. However, patients with enthesitis-related JIA appear to have relatively poor prognosis together with, in accordance with previous accounts [253,254,355], patients with RF+ polyarthritis. Those with systemic JIA were reported to have the largest variation in achievement of clinically inactive disease and remission, ranging from 0% [369] to 100% [255], irrespective of time followed. This large variation likely stems from the different outcome definitions that capture variable elements of systemic disease, rather than any particularly diverse outcomes experienced by patients with systemic JIA within different studies.

### 6.1.6.1 Strengths and Limitations

This was the first review of remission in JIA conducted systematically. That all published estimates from relevant inception cohorts were included lends these estimates far more generalisable to the general population of patients with JIA than any from previous reviews. Twelve years have passed since the introduction of Wallace's preliminary criteria [165] and five since the introduction of the ACR 2011 criteria [185] which allows assessment of definition uptake within clinical studies. No study has so far published outcomes described using the recently proposed JADAS clinically inactive disease cut-offs [168,186]. Future work

should encourage the uptake of these more novel sets of criteria to assess their performance in real-world datasets.

Limitations of the current review related to study quality with regards to selection and missing data biases. This review highlights that few inception cohorts have reported on the outcome of disease remission or clinically inactive disease. This may reflect a paucity of studies, or that existing studies either do not have the available data or have not been recruiting CYP long enough to report these outcomes. Heterogeneity between studies which have been published hindered the comparability of data extracted. It is noted that many studies were from Scandinavia, and therefore the results may not be directly applicable to countries with significantly different health care systems or access to treatments. Further research needs to assess the outcomes in other populations not included in this review. In addition, the vast majority of studies did not deal with missing outcome data appropriately and as evidenced by Fantini et al, patients lost to follow-up are more likely to be in remission than those who continue presenting to clinic [250]. By excluding patients with incomplete data at baseline or not imputing their outcome data using appropriate methods, the frequencies of remission are likely to be underestimated in these studies. In addition, approximately a third of studies either did not have at least 80% participation or did not compare patients that consented and those that refused to participate. However, these selection biases were minimised by only including inception cohorts in the current review.

Few studies reported the cumulative achievement of clinically inactive disease or remission. Since the disease course in JIA is one of remitting and relapse [269], estimates of 'ever' rather than 'current' remission may give a better overall picture of disease activity in affected CYP. In addition, the number of repeated periods in remission or length of sustained remission over study follow-up would ideally be captured. In order to explore if the current estimates are accurate and to increase the knowledge of the patterns of remission in JIA, further work should explore these outcomes. In addition, the changes in achievement of these states could not be assessed between pre- and post-biologics eras. Recruitment to many of the studies spanned the introduction of biologic therapies and the uptake of more aggressive treatment strategies. It was therefore unclear which patients in each study had been exposed to these new strategies and which had not been. This review could therefore not associate specific therapies with achievement of clinically inactive disease or remission, particularly since wider and earlier use of methotrexate in the same period as the introduction of biologic therapies [374] may also have influenced results.

The largest limitation of the review was the inability to pool or directly compare results. This stemmed from the vast number of sets of clinically inactive disease and remission criteria. The number of criteria sets continues to increase and it is not yet clear which should be designated, if any, as main set of outcome criteria for use in observational research in JIA. Since there is no 'gold-standard' for remission in JIA, current published criteria sets have been validated against different surrogate measures. It is therefore unclear if the same construct is being assessed across sets of criteria. Further work should assess the degree of overlap between these sets of criteria through comparisons in a single population at a common time point.

### 6.1.7    Conclusions

In this first systematic review of remission in JIA, the frequency of current remission increased with increasing disease duration from 7% at 18 months to around 40% after at least 10 years. Large variation in estimates existed, largely driven by differences in the 13 sets of outcome criteria utilised. Patients with persistent oligoarticular disease had high achievement of remission with those in RF+ polyarticular category the lowest.

### 6.1.8    Acknowledgements

### 6.1.9    Disclosures

The authors declare no conflicts of interest.

### 6.1.10  Supplementary Materials

No review protocol has been previously published.

**Supplementary Table 1.** Search strategy and results for each database

| # | Search History | Results |
|---|---|---|
| **Medline** | | |
| 1 | exp ARTHRITIS, JUVENILE/ cl, di, dt, ep, ge, im, pc, su, th. | 5894 |
| 2 | JIA | 1880 |
| 3 | CHILD* or ADOLESCENT | 2712565 |
| 4 | ARTHRITIS/ cl, di, dt, ep, ge, pc, rh, su, th | 12146 |
| 5 | 3 and 4 | 1790 |
| 6 | 1 or 2 or 5 | 8235 |
| 7 | exp REMISSION, INDUCTION | 32934 |
| 8 | exp REMISSION, SPONTANEOUS/ bl, ci, di, dt, ep, im, pp, rt, th | 232 |
| 9 | REMISSION | 110391 |
| 10 | DISEASE ACTIVITY | 25038 |
| 11 | LOW or MINIMAL or ABSEN* or QUIESCE* | 2139027 |
| 12 | 10 adj3 11 | 753 |
| 13 | DISEASE OUTCOME* | 5655 |
| 14 | INACTIVE DISEASE | 1173 |
| 15 | ACCEPTABLE SYMPTOM STATE | 47 |
| 16 | 7 or 8 or 9 or 12 or 13 or 14 or 15 | 118118 |
| 17 | 6 and 16 | 546 |
| 18 | Limit 17 to (CLINICAL TRIAL, ALL or RANDOMIZED CONTROLLED TRIAL) | 74 |
| 19 | Limit 17 to CASE REPORTS | 76 |
| 20 | Limit 17 to (CLINICAL CONFERENCE or CONGRESSES) | 1 |
| 21 | Limit 17 to (META ANALYSIS or REVIEW or SCIENTIFIC INTEGRITY REVIEW or SYSTEMATIC REVIEWS) | 90 |
| 22 | 17 not (18 or 19 or 20 or 21) | 318 |
| 23 | Limit 22 to English language | **287** |
| **Embase** | | |
| 1 | exp JUVENILE RHEUMATOID ARTHRITIS/ di, dm, dr, dt, ep, rh, su, th | 6697 |
| 2 | JIA | 4807 |
| 3 | CHILD* or ADOLESCENT | 2630948 |
| 4 | ARTHRITIS/ di, dm, dr, dt, ep, rh, su, th | 16033 |
| 5 | 3 and 4 | 1546 |
| 6 | 1 or 2 or 5 | 11574 |
| 7 | exp REMISSION | 88438 |
| 8 | DISEASE ACTIVITY | 53363 |
| 9 | LOW or MINIMAL or ABSEN* or QUIESCE* | 2908940 |
| 10 | 8 and 9 | 11304 |
| 11 | DISEASE OUTCOME* | 8630 |
| 12 | INACTIVE DISEASE | 1910 |
| 13 | ACCEPTABLE SYMPTOM STATE | 115 |
| 14 | 7 or 10 or 11 or 12 or 13 | 107149 |
| 15 | 6 and 15 | 1259 |
| 16 | Limit 15 to (CLINICAL TRIAL or RANDOMIZED CONTOLLED TRIAL or CONTROLLED CLINICAL TRIAL or PHASE 1 CLINICAL TRIAL or PHASE 2 | 154 |

| | CLINICAL TRIAL or PHASE 3 CLINICAL TRIAL or PHASE 4 CLINICAL TRIAL) | |
|---|---|---|
| 17 | Limit 15 to (CONFERENCE ABSTRACT or CONFERENCE PAPER or CONFERENCE PROCEEDING or CONFERENCE REVIEW) | 554 |
| 18 | Limit 15 to (META ANALYSIS or SYSTEMATIC REVIEW) | 13 |
| 19 | 15 not (16 or 17 or 18) | 578 |
| 20 | Limit 19 to English language | **531** |
| **Pubmed** | | |
| 1 | JUVENILE or CHILD* or ADOLESCENT | 3025294 |
| 2 | ARTHRITIS or POLYARTHRIT* or OLIGOARTHRIT* OR STILL'S | 263312 |
| 3 | 1 AND 2 | 11365 |
| 4 | REMISSION | 117611 |
| 5 | INACTIVE DISEASE | 10333 |
| 6 | DISEASE ACTIVITY and (LOW or MINIMAL or ABSEN* or QUIESCE*) | 55572 |
| 7 | DISEASE OUTCOME* | 6623 |
| 8 | ACCEPTABLE SYMPTOM STATE | 128 |
| 9 | 4 or 5 or 6 or 7 or 8 | 186094 |
| 10 | 3 and 9 | 1637 |
| 11 | Limit 10 to Journal Article | 1602 |
| 12 | Limit 11 to publication after 01/01/2013 | 272 |
| 13 | Limit 12 to English Language | 262 |
| 14 | Limit 13 to not medline[sb] | **74** |

**Supplementary Table 2.** The Quality Assessment (QA) Tool adapted from Pasma and others [360] and the Cochrane Collaboration tool for assessing risk of bias [361] to assess bias in selected articles

| Measure of quality assessed | Coding framework | | |
|---|---|---|---|
| Appropriate methods to select participants | | | |
| 1. Sampling frame, age and sex of sample described | Yes | No | Don't know |
| **2. >80% participation or comparison of consents and refusals** | Yes | No | Don't know |
| Appropriate methods to measure remission | | | |
| **3. Measure of remission reproducible** | Yes | No | Don't know |
| 4. Remission measure | Validated objective | Non-validated objective | Non-validated subjective |
| Appropriate methods to reduce bias in design or analysis | | | |
| **5. Serious selection bias reduced by consecutive or stratified sampling** | Yes | No | Don't know |
| 6. Proportion of patients in remission was a primary outcome | Yes | No | Don't know |
| **7. Serious bias arising from missing data reduced by adhering to at least one of the following:** <br> - No missing remission data <br> - Reason for missing data likely unrelated to outcome <br> - The proportion of missing remission data not enough to have a clinically relevant impact on results <br> - Missing data imputed using appropriate methods <br> **Criteria for 'don't know':** <br> - Numbers censored or with incomplete remission data not reported | Yes | No | Don't know |
| Conflict of interest | | | |
| 8. Conflict of interest declaration | Yes | No | Don't know |

Questions in bold refer to 'essential' items.

**Supplementary Table 3.** Full results from the quality assessment tool for all selected articles

| | 1 | 2 (E) | 3 (E) | 4 | 5 (E) | 6 | 7 (E) | 8 | Total: | Total essentials | Overall article quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Guzman et al., 2014 [5] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | Yes | **Yes** | Yes | 7 | **4** | **High** |
| Berntson et al., 2014 [280] | Yes | **Yes** | **Yes** | Validated objective | **No** | No | **Yes** | Yes | 6 | **3** | **High** |
| Berntson et al., 2013 [276] | Yes | **Don't know** | **Yes** | Validated objective | **Yes** | Yes | **No** | Yes | 6 | **2** | **Low** |
| Shen et al., 2013 [30] | Yes | **Yes** | **Yes** | Validated objective | **Yes** | No | **Yes** | Yes | 7 | **4** | **High** |
| Shen et al., 2013 [362] | Yes | **Don't know** | **Yes** | Validated objective | **Yes** | Yes | **No** | Yes | 6 | **2** | **Low** |
| Nordal et al., 2011 [275] | Yes | **Don't know** | **Yes** | Validated objective | **Yes** | Yes | **No** | Yes | 6 | **2** | **Low** |
| Oen et al., 2009 [273] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | Yes | **No** | Yes | 6 | **3** | **High** |
| Berntson et al., 2007[364] | Yes | **Don't know** | **Yes** | Non-validated objective | **Don't know** | No | **No** | No | 2 | **1** | **Low** |
| Gäre et al., 1993 [366] | Yes | **Don't know** | **Yes** | Non-validated objective | **Yes** | Don't know | **No** | No | 3 | **2** | **Low** |
| Bertilsson et al., 2013 [257] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | Yes | **No** | Yes | 6 | **3** | **High** |
| Bertilsson et al., 2012 [363] | Yes | **Yes** | **No** | Non-validated subjective | **Yes** | Yes | **No** | Yes | 5 | **2** | **Low** |
| Flatø et al., 1998 [369] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | Yes | **No** | Yes | 6 | **3** | **High** |
| Gäre et al., 1995 [255] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | No | **No** | Yes | 5 | **3** | **High** |
| Gäre et al., 1995 [365] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | No | **No** | No | 4 | **3** | **Low** |
| Padeh et al., 2013 [367] | Yes | **Don't know** | **Yes** | Validated objective | **Yes** | Yes | **No** | No | 5 | **2** | **Low** |
| Selvaag et al., 2006 [368] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | Yes | **No** | Yes | 6 | **3** | **High** |
| Kotaniemi et al., 2002 [268] | Yes | **Yes** | **Yes** | Non-validated objective | **Yes** | Yes | **No** | No | 5 | **3** | **High** |

E: Essential items. For column 4, one point is awarded where validated objective criteria was implemented. For all other columns, only an answer of 'Yes' scores one point. A high quality article was defined as scoring 'yes' on at least three of the four essential questions or scoring at least five points overall.

**Supplementary Table 4.** The frequencies of remission across ILAR subtypes in selected articles

| Author | Remission criteria | Disease duration at assessment | When remission assessed | Entire cohort | | Percent in remission within disease subtypes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Percent ever remission (%) | Percent current remission (%) | Systemic | Oligo | RF- Poly | RF+ Poly | Poly in ERA general | in ERA | PsA | U. |
| **Multi-centre** | | | | | | | | | | | | | |
| Guzman et al., 2014 [5] | Investigator defined ID and CR | 5 years | Throughout follow-up | 1 year: 45 (ID) 2 yrs: 78 (ID) 4 (CR) 3 yrs: 85 (ID) 13 (CR) 4 yrs: 92 (ID) 28 (CR) 5 yrs: 95 (ID) 41 (CR) | - | 1yr: 45 (ID) 2yrs: 71 (ID) 4.8 (CR) 3yrs: 73 (ID) 11 (CR) 4yrs: 85 (ID) 29 (CR) 5yrs: 85 (ID) 47 (CR) | 1yr: 61 (ID) 2yrs: 86 (ID) 7.6 (CR) 3yrs: 92 (ID) 21 (CR) 4ys: 96 (ID) 41 (CR) 5yrs: 96 (ID) 58 (CR) | 1yr: 34 (ID) 2yrs: 71 (ID) 1.1 (CR) 3yrs: 78 (ID) 3.2 (CR) 4yrs: 88 (ID) 7.7 (CR) 5yrs: 97 (ID) 14 (CR) | 1yr: 22 (ID) 2yrs: 48 (ID) 0 (CR) 3yrs: 67 (ID) 0 (CR) 4yrs: 79 (ID) 0 (CR) 5yrs: 93 (ID) 0 (CR) | - | 1yr: 34 (ID) 2yrs: 72 (ID) 1.9 (CR) 3yrs: 87 (ID) 5.8 (CR) 4yrs: 92 (ID) 28 (CR) 5yrs: 93 (ID) 47 (CR) | 1yr: 46 (ID) 2yrs: 91 (ID) 7.2 (CR) 3yrs: 93 (ID) 21 (CR) 4yrs: 92 (ID) 47 (CR) 5yrs: 100 (ID) 47 (CR) | 1yr: 33 (ID) 2yrs: 78 (ID) 1.2 (CR) 3yrs: 84 (ID) 11 (CR) 4yrs: 89 (ID) 30 (CR) 5yrs: 100 (ID) 46 (CR) |
| Berntson et al., 2014 [280] | Wallace's preliminary criteria | 8 years | End of follow-up | - | 67 (ID) | - | - | - | - | - | - | - | - |
| Berntson et al., 2013 [276] | Wallace's preliminary criteria | 8 years | End of follow-up | - | 41 (CR) | - | - | - | - | - | - | - | - |
| Shen et al., 2013 [30] | Wallace's preliminary criteria | Median 8.7 years (IQR 6.0 to 12.5) | Throughout and end of follow-up | 52 (CR) | 15 (CRM) 45 (CR) | End of follow-up: 14 (CRM) 54 (CR) Throughout: 50 (CRM) | End of follow-up: Pers: 19 (CRM) 66 (CR) Ext: 23 (CRM) 39 (CR) Throughout: Pers: 69 (CR) Ext: | End of follow-up: 13 (CRM) 48 (CR) Throughout: 48 (CR) | End of follow-up: 33 (CRM) 11 (CR) Throughout: 11 (CR) | - | End of follow-up: 11 (CRM) 33 (CR) Throughout: 41 (CR) | End of follow-up: 33 (CRM) 67 (CR) Throughout: 67 (CR) | End of follow-up: 15 (CRM) 45 (CR) Throughout: 28 (CR) |

| Author | Remission criteria | Disease duration at assessment | When remission assessed | Entire cohort | | Percent in remission within disease subtypes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Percent ever remission (%) | Percent current remission (%) | Systemic | Oligo | RF- Poly | RF+ Poly | Poly in general | ERA | PsA | U. |
| | | | | | | | 62 (CR) | | | | | | |
| Bertilsson et al., 2013 [257] | Investigator defined ID and CR | 5 years<br>17 years | At 5 and 17 year follow-up | - | 5 years:<br>20 (ID)<br>38 (CR)<br><br>17 years:<br>19 (ID)<br>40 (CR) | 33 (ID)<br>50 (CR) | 5yrs:<br>18 (ID)<br>44 (CR)<br>17yrs:<br>31 (ID)<br>43 (CR) | - | - | 5yrs:<br>24 (ID)<br>24 (CR)<br>17yrs:<br>6 (ID)<br>39 (CR) | 5yrs:<br>0 (ID)<br>0 (CR)<br>17yrs:<br>0 (ID)<br>17 (CR) | 5yrs:<br>0 (ID)<br>25 (CR)<br>17yrs:<br>25 (ID)<br>25 (CR) | - |
| Shen et al., 2013 [362] | Wallace's preliminary criteria | 1.5 years | End of follow-up | - | 53 (ID) | 67 (ID) | 90 (ID) | - | - | 44 (ID) | 39 (ID) | - | 23 (MDA)<br>47 (CR) |
| Bertilsson et al., 2012 [363] | Investigator defined ID and CR | 5 years | End of follow-up | - | 25 (ID)<br>34 (CR) | - | 28 (ID)<br>39 (CR) | - | - | 21 (ID)<br>24 (CR) | 0 (ID)<br>0 (CR) | 0 (ID)<br>50 (CR) | - |
| Nordal et al., 2011 [275] | Wallace's preliminary criteria<br>PGA=0<br>PGE=0 | Median 8.2 years (IQR 7.0 to 12.3) | End of follow-up | - | 54 (PGA=0)<br>50 (PGE=0)<br>9 (CRM)<br>42 (CR) | 75 (PGA=0)<br>77 (PGE=0)<br>0 (CRM)<br>83 (CR) | Pers:<br>73 (PGA=0)<br>74 (PGE=0)<br>3.2 (CRM)<br>66 (CR)<br>Ext:<br>41 (PGA=0)<br>33 (PGE=0)<br>16 (CRM)<br>21 (CR) | 46 (PGA=0)<br>39 (PGE=0)<br>14 (CRM)<br>28 (CR) | 33 (PGA=0)<br>33 (PGE=0)<br>0 (CRM)<br>33 (CR) | - | 42 (PGA=0)<br>39 (PGE=0)<br>8.2 (CRM)<br>31 (CR) | 58 (PGA=0)<br>62 (PGE=0)<br>23 (CRM)<br>23 (CR) | 49 (PGA=0)<br>37 (PGE=0)<br>6.3 (CRM)<br>41 (CR) |
| Oen et al., 2009 [273] | Wallace's preliminary criteria | Mean months | 6 End of follow-up | - | 33 (ID) | 27 (ID) | 46 (ID) | 19 (ID) | 8 (ID) | - | 19 (ID) | 35 (ID) | 32 (ID) |
| Berntson et al., 2007 [364] | No active joints<br>PGA=0<br>PGE=0 | 8 years | A random point throughout follow-up | - | 45 (No active joints)<br>20 (PGA=0)<br>35 (PGE=0) | - | - | - | - | - | - | - | - |
| Gäre et al., 1995 [255] | Investigator defined ID and CR | Median years (range 1.5 to 21.9) | 7 End of follow-up | - | 20 (ID)<br>31 (CR) | 5yrs:<br>25 (ID)<br>75 (CR)<br>17yrs:<br>25 (ID)<br>75 (CR) | 52 (Pers; CR) | - | - | 48 (ID) | 40 (ID) | 0 (ID) | - |

| Author | Remission criteria | Disease duration at assessment | When remission assessed | Entire cohort | | Percent in remission within disease subtypes | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Percent ever remission (%) | Percent current remission (%) | Systemic | Oligo | RF- Poly | RF+ Poly | Poly general | in ERA | PsA | U. |
| Gäre et al., 1995 [365] | No active joints | Median 7 years (range 1.5 to 21.9) | End of follow-up | - | 37 | - | - | - | - | - | - | - | - |
| Gäre et al., 1993 [366] | Investigator defined ID and CR | Group 1: mean 8.1 years (SD: 4.4) Group 2: Mean 5 years (SD: 0.5) | End of follow-up | - | Group 1: 25 (ID) 37 (CR) Group 2: 31 (ID) 43 (CR) | - | - | - | - | - | - | - | - |
| Single centre | | | | | | | | | | | | | |
| Padeh et al., 2013 [367] | Wallace's preliminary criteria | Mean 1.5 years (SD: 0.5) | End of follow-up | - | 7 (CR) | - | - | - | - | - | - | - | - |
| Selvaag et al., 2006 [368] | Investigator defined CR | Mean 3.2 years (SD: 0.4) | End of follow-up | - | 26 | 29 | 39 (Pers) 6 (Ext) | 16 | 0 | - | 0 | 20 | - |
| Kotaniemi et al., 2002 [268] | Investigator defined CR | Mean 4.5 years | End of follow-up | - | 37 | - | - | - | - | - | - | - | - |
| Flatø et al., 1998 [369] | ACR 1981 RA remission criteria (ID) sustained for ≥6 months (CR) | Mean 9.7 years (SD: 2.1) | End of follow-up | - | 60 (ID) 47 (CR) | 0 | 84 (Pers) 28 (Ext) | - | - | 65 | 33 | 71 | - |

Oligo: Oligoarticular JIA; RF- Poly: Rheumatoid factor negative polyarticular JIA; RF+ Poly: Rheumatoid factor positive polyarticular JIA; ERA: Enthesitis-related JIA; PsA: Psoriatic JIA, U:

Undifferentiated JIA; PGA: Physician's global assessment of disease activity; PGE: Parental global assessment of disease activity; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ACR:

American College of Rheumatology; RA: Rheumatoid arthritis; CR: Clinical remission off medication; CRM: Clinical remission on medication, SD: Standard deviation, IQR: Interquartile range.

## 6.2 How Common is Clinically Inactive Disease in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis? The Importance of Definition

**Published in Annals of the Rheumatic Diseases**

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**Word count (excluding references):** 3158

**Key words:** Juvenile Idiopathic Arthritis, Inactive disease, Minimal disease activity, Paediatric rheumatology, Epidemiology

### 6.2.2  Abstract

**Objectives:** Many criteria for clinically inactive disease (CID) and minimal disease activity (MDA) have been proposed for juvenile idiopathic arthritis (JIA). It is not known to what degree each of these criteria overlap within a single patient cohort. This study aimed to compare the frequency of MDA and CID across different criteria in a cohort of children and young people (CYP) with JIA at one year following presentation.

**Methods:** The Childhood Arthritis Prospective Study recruits CYP at initial presentation to paediatric or adolescent rheumatology in seven UK centres. CYP recruited between October 2001 and December 2013 were included. The proportions of CYP with CID and MDA at one year were calculated using four investigator-defined and eight published composite criteria. Missing data were accounted for using multiple imputation under different assumptions.

**Results:** In a cohort of 1415 CYP, 67% patients had no active joints at one year. Between 48% and 61% achieved MDA and between 25% and 38% achieved CID using published criteria. Overlap between criteria varied. Of 922 patients in MDA by either the original composite criteria, Juvenile Arthritis Disease Activity Score (JADAS) or clinical JADAS cut-offs, 68% were classified as in MDA by all 3 criteria. Similarly, 44% of 633 CYP with CID defined by either Wallace criteria or the JADAS cut-off were in CID according to both criteria.

**Conclusion:** In a large JIA prospective inception cohort, a majority of patients have evidence of persistent disease activity after one year. Published criteria to capture MDA and CID do not always identify the same groups of patients. This has significant implications when defining and applying treat-to-target strategies.

### 6.2.3  Introduction

Juvenile idiopathic arthritis (JIA) represents the most common inflammatory rheumatic disease of childhood [16]. To minimise pain and disability associated with active disease, one goal for all children and young people (CYP) with JIA is clinically inactive disease (CID), meaning absence of active inflammation [165]. However, CID is not always achievable and a more realistic target may be minimal disease activity (MDA), meaning limited evidence of active inflammation [187]. Defining either of these states in such a heterogeneous disease is challenging; there is no single diagnostic test for either state and as such multiple criteria have been proposed.

Simple clinical criteria for CID include no active joints or a score of zero on the physician (PGA) or parental (PGE) global evaluation. These single targets are easy to apply in clinical practice as part of the core outcome criteria for JIA [161]. However, each alone may not capture the full spectrum of disease. Composite disease activity scores are more precise than their individual components, capturing multiple domains of disease activity and potentially increasing the statistical power of clinical trials [375]. Over the past 15 years, a number of composite criteria have been proposed and variably validated in JIA patient populations. These include Wallace's preliminary criteria for CID and remission on and off medication [165], the Juvenile Arthritis Disease Activity Score (JADAS)  and clinical JADAS (cJADAS) cut-offs for MDA, CID and remission [168,186] and the American College of Rheumatology (ACR) preliminary criteria for CID [185] (Table 21).

The aim of developing criteria for CID and MDA has been to better define the states of low disease activity as well as standardise outcome criteria across clinical trials and observational research [165]. However, differences in patients identified by each set of criteria may contribute to the large variation in CID achievement described between cohorts observed in the literature [254]. One study compared the frequency of CID according to a modified ACR preliminary criteria [185] against achieving no active joints or zero on the PGA, PGE or child global assessments of disease activity. Within this single population, achievement of CID according to each set of criteria ranged from 19 to 68% [376]. None of these single or modified composite criteria used in the study described have been validated in JIA and to date, no studies have directly compared published criteria within a single population to understand if they define similar groups of CYP.

Multiple high quality studies support the efficacy of accelerated or targeted early treatment pathways in adult inflammatory arthritis (particularly RA) [377-380]. Treating to target should

lead to similar improvements in clinical outcomes for patients with JIA, but requires valid, feasible and consistent treatment targets across different studies.

This study aims to apply single and published composite criteria for CID and MDA in a single patient population at a common time point: one year following initial presentation to rheumatology. The proportions of CYP reaching these states could then be compared between criteria of CID and MDA. Specifically, the study objectives are to (1) estimate the frequency of CID and MDA at one year following initial presentation; (2) investigate the differences in achievement of these disease states across International League of Associations for Rheumatology (ILAR) subtypes and; (3) investigate if similar groups of CYP are captured by the different CID/MDA criteria.

**Table 21.** Published clinically inactive disease and minimal disease activity criteria for JIA

| Criteria | Components included | | | | | | | Requirement for classification of CID or MDA |
|---|---|---|---|---|---|---|---|---|
| | AJC | PGA | PGE | ESR/CRP | Systemic features | Uveitis | Morning stiffness | |
| Composite CID criteria | | | | | | | | |
| Wallace's preliminary criteria [165] | ✓ | ✓ | | ✓ | ✓ | ✓[1] | | Normal ESR/CRP and all other values at zero or not present |
| ACR preliminary criteria [185] | ✓ | ✓ | | ✓ | ✓ | ✓[2] | ✓ | Normal ESR/CRP, morning stiffness≤15mins and all other values at zero or not present |
| JADAS [168] | ✓ | ✓ | ✓ | ✓ | | | | JADAS≤1 |
| cJADAS [186] | ✓ | ✓ | ✓ | | | | | cJADAS≤1 |
| Composite MDA criteria | | | | | | | | |
| MDA (Magni-Manzoni) [187] | ✓ | ✓ | ✓[3] | | | | | Persistent oligoarticular: AJC=0, PGA≤2.5 Extended oligoarticular, polyarticular and systemic JIA: ACJ≤1, PGA≤3.4, PGE≤2.1 |
| JADAS [168] | ✓ | ✓ | ✓ | ✓ | | | | Oligoarticular course: JADAS≤2.0 Polyarticular course: JADAS≤3.8 |
| cJADAS [186] | ✓ | ✓ | ✓ | | | | | Oligoarticular course: cJADAS≤1.5 Polyarticular course: cJADAS≤2.5 |

1. Inactive uveitis was not defined 2. Inactive uveitis as defined by the SUN working group [381] 3. Not required for persistent oligoarticular JIA. PGA: CID: Clinically inactive disease, MDA: Minimal disease activity, AJC: Active joint count, PGA: Physician's global assessment of disease activity, PGE: Parental/child global evaluation of disease activity, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, JADAS: Juvenile Arthritis Disease Activity Score, cJADAS: clinical JADAS, ACR: American College of Rheumatology.

### 6.2.4   Methods

#### 6.2.4.1 Study Population

CYP were participants in the Childhood Arthritis Prospective Study (CAPS), a UK multi-centre inception cohort established in 2001. Details of this cohort have been described previously [382]. To date, the cohort exceeds 1500 patients with childhood-onset inflammatory arthritis. CAPS was approved by the Northwest Multicentre Research Ethics Committee and written consent from parents/guardians was attained for all participants. Where able, CYP also provided assent.

Patients were included in the current study if they had a physician diagnosis of JIA and had been recruited to the cohort before December 2013, to allow at least one year of follow-up. Prevalent cases and CYP with no returned study report forms were excluded.

#### 6.2.4.2 Data Collection

The baseline date was that of first presentation to paediatric or adolescent rheumatology in one of seven centres in the UK. Baseline and one year follow-up data were collected from medical case notes, nurse and parent/patient questionnaires. Age and gender were recorded at baseline. Data from medical case notes included rheumatologic diagnosis and ILAR category. ILAR category was defined using study data available at one year to allow CYP to "settle" into a category. If ILAR category was missing at one year, the most recent previously collected ILAR category was used. Data from case notes also included numbers of active and limited joints (maximum 71), a 10cm visual analogue scale (VAS) assessing physician's global assessment of disease activity, extra-articular disease features, results of laboratory investigations including erythrocyte sedimentation rate (ESR)(mm/hr) and C-reactive protein (CRP) (mg/L) and medication details including both anti-rheumatic and other therapeutics. Parent questionnaires included a Childhood Health Assessment Questionnaire (CHAQ), and two 10cm VAS measures for pain and wellbeing, respectively. Young people over the age of 11 have the option to self-report.

#### 6.2.4.3 Outcomes of CID and MDA

Outcomes comprising a single criterion included no active joints and zero on the PGA or PGE. Published composite outcomes for the current analysis included CID according to the Wallace's preliminary criteria [165], JADAS [168] and cJADAS [186] and MDA according to the JADAS [168], cJADAS [186] and the original Magni-Manzoni criteria [187] (Table 21). The sets of criteria were applied in full across all ILAR subtypes. As CAPS did not capture

daily morning stiffness over most of the period of recruitment to this study, the ACR preliminary criteria for CID [185] were not applied.

### 6.2.4.4 Statistical Analyses

All outcomes were calculated from extracted data items at the one year follow-up visit. The frequency and proportion of outcomes in all patients and within ILAR subtypes were reported. In addition, the overlap between patient groups identified by multiple outcomes was explored.

The primary analysis assumed that some data were missing (Table 23) in a 'missing-not-at-random' (MNAR) mechanism. CYP with missing data were split into six groups: Those 1) discharged 'well', 2) discharged following repeat non-attendance, 3) transferred to other clinics, 4) moved home address or unknown reason for discharge, 5) lost to follow-up in CAPS and 6) follow-up form completed but with incomplete data. The following assumptions were made regarding these groups: Patients were in CID according to all outcome criteria (groups one, two, five and three if transferred to adult services) or patients had normal laboratory criteria with other missing data missing at random (MAR) (group six). Unless assumed 'well', all other missing data were imputed via multiple imputation over 20 iterations assuming data MAR.

Secondary analyses included a complete case analysis as well as a most extreme scenarios analysis, which assumed all CYP with missing data or forms were either entirely in active disease or entirely in CID/MDA for each set of criteria.

## 6.2.5   Results

### 6.2.5.1 Patient Cohort

Up to December 2013, 1510 patients had been recruited to CAPS. Of these, 95 were excluded (60 were not diagnosed with JIA, three were prevalent cases and 32 had no available data), leaving 1415 CYP for analysis.

Sixty-five percent of CYP were female and median age at first presentation was 8 years (interquartile range (IQR) 3.5 to 12 years). The most common ILAR subtypes were oligoarticular (50%) and RF-negative polyarticular JIA (21%) (Table 22). Median baseline active joint count was two (IQR 1 to 6) with median physician global assessment at 2.9cm (IQR 1.5 to 5.0) (Table 22).

**Table 22.** Baseline and one year characteristics of the cohort

| Characteristic | No. patients with available baseline data (%) | N(%) or median (IQR) at baseline | No. patients with available 1yr data (%) | N(%) or median (IQR) at one year |
|---|---|---|---|---|
| Female | 1415 (100) | 917 (65) | | |
| White or Caucasian | 1380 (98) | 1238 (90) | | |
| Age at onset (years) | 1396 (99) | 6.6 (2.7 to 11) | | |
| Age at first presentation (years) | 1409 (100) | 7.7 (3.5 to 12) | | |
| Symptom duration at diagnosis (months) | 1391 (98) | 5.4 (2.8 to 12) | | |
| **ILAR subtype:** | | | | |
| Systemic | | 96 (6.7) | | |
| Oligoarticular | | 707 (50) | | |
| RF- Polyarticular | | 292 (21) | | |
| RF+ Polyarticular | 1415 (100) | 49 (3.5) | | |
| Enthesitis-related | | 77 (5.4) | | |
| Psoriatic | | 97 (6.9) | | |
| Undifferentiated | | 97 (6.9) | | |
| **Score components:** | | | | |
| Active joint count | 1269 (90) | 2 (1 to 5) | 1000 (71) | 0 (0 to 1) |
| Limited joint count | 1269 (90) | 1 (1 to 3) | 1000 (71) | 0 (0 to 1) |
| CHAQ score | 972 (69) | 0.8 (0.1 to 1.4) | 936 (66) | 0.3 (0.0 to 0.9) |
| PGA score (cm) | 939 (66) | 2.9 (1.5 to 5.0) | 819 (58) | 0.5 (0.0 to 1.8) |
| PGE score (cm) | 936 (66) | 2.3 (0.5 to 5.0) | 928 (66) | 0.6 (0.1 to 2.9) |
| ESR (mm/hr) | 889 (63) | 21 (7 to 49) | 269 (19) | 8 (4 to 19) |
| Normal ESR (<20mm/hr) | 889 (63) | 441 (50) | 269 (19) | 212 (79) |
| CRP (mg/L) | 844 (60) | 7 (4 to 27) | 238 (17) | 4 (3 to 7) |
| Normal CRP (dependent on hospital assay) | 844 (63) | 482 (57) | 238 (19) | 202 (85) |
| Diagnosis of uveitis | 294 (21) | 11 (3.7) | 252 (18) | 20 (7.9) |
| Systemic features present (systemic JIA only) | 94 (98) | 89 (95) | 70 (73) | 39 (56) |
| **Treatments in the first year** | | | | |
| NSAID | | | | 1040 (73) |
| Steroid* | | | 1415 (100) | 1050 (74) |
| DMARD | | | | 670 (47) |
| Biologic | | | | 115 (8) |

Data are presented as n (%) or median (IQR) where appropriate. *Steroids administered orally/IV/intra-articular. CHAQ: Childhood Health Assessment Questionnaire; PGA: Physician global assessment of disease activity; PGE: Parental global evaluation of disease activity; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ILAR: International League of Associations for Rheumatology; RF: Rheumatoid factor; NSAID: Non-steroidal anti-inflammatory drug; DMARD: Disease-modifying anti-rheumatic drug

### 6.2.5.2 Achievement of C ID or MDA

The one-year follow-up form was not completed in 85 CYP. Fifty-nine had been discharged from rheumatology within the first year, including 24 who had been discharged 'well'. Others had moved to another paediatric or adolescent clinic (n=11), moved to adult services (n=11) failed to attend (n=30) or were lost to follow-up (n=9). These patients did not differ significantly at baseline from those with one year data available, except for PGA score (available median PGA 2.9cm, IQR 1.6 to 5.1,  missing median PGA 2.0cm, IQR 1.1 to 3.1, p=0.004).

Overall, 72% (95% confidence interval (CI): 68 to 74) of patients achieved CID or MDA according to at least one set of criteria, with estimates ranging from 25% using Wallace's preliminary criteria to 67% if only an active joint count was used. Using composite criteria, fewer CYP achieved CID (range 25-38%) compared with MDA (range 48-61%) (Table 23). Imputed estimates consistently exceeded those from complete case analysis (Table 23).

**Table 23.** The frequency of CID and MDA using Complete Case and Multiple Imputation analyses

| Outcome criteria | Primary outcome: Percent in CID/MDA following imputations assuming data MNAR (%; 95%CI) (n=1415) | Percent in CID/MDA using complete case analysis | | Percent in CID/MDA using most extreme scenarios (n=1415) | |
|---|---|---|---|---|---|
| | | Percent (%) | How many CYP could be categorised | Minimum | Maximum |
| **Single criteria for CID** | | | | | |
| Discharge from rheumatology as 'well' within the first year following presentation | NA | 1.7 | 1366 | NA | NA |
| Active joint count = 0 | 67 (64, 69) | 48 | 1000 | 46 | 75 |
| Physician global assessment = 0 | 36 (33, 39) | 32 | 819 | 19 | 61 |
| Parental global evaluation = 0 | 28 (25, 31) | 23 | 928 | 15 | 50 |
| **Composite criteria for CID** | | | | | |
| Wallace's preliminary criteria for CID | 25 (22, 28) | 4.5 | 810 | 1.2 | 45 |
| CID using JADAS10 | 38 (35, 41) | 5.1 | 688 | 2.5 | 54 |
| CID using JADAS71 | 38 (35, 41) | 5.1 | 688 | 2.5 | 54 |
| CID using cJADAS10 | 38 (35, 42) | 26 | 880 | 15 | 54 |
| **Composite criteria for MDA** | | | | | |
| MDA using JADAS10 | 53 (49, 56) | 13 | 522 | 5.0 | 68 |
| MDA using JADAS71 | 53 (49, 56) | 13 | 522 | 5.0 | 68 |
| MDA using cJADAS10 | 48 (45, 51) | 35 | 807 | 20 | 63 |
| MDA criteria (Magni-Manzoni) | 61 (58, 64) | 47 | 740 | 25 | 73 |
| **Cumulative achievement** | | | | | |
| Any single/composite CID or MDA* | 72 (68, 74) | 56 | 1212 | 48 | 89 |
| Any composite CID | 42 (38, 45) | 25 | 1020 | 18 | 76 |
| Any composite MDA | 65 (62, 68) | 45 | 859 | 27 | 78 |

*Not including discharged 'well'; CID: Clinically inactive disease, MDA: Minimal disease activity, JADAS: Juvenile Arthritis Disease Activity Score, cJADAS: JADAS

excluding erythrocyte sedimentation rate, CI: Confidence Interval, MNAR: Missing not at random, CYP: Children and young people

### Estimates of CID across Criteria

At one year following initial presentation to rheumatology, 42% (95% CI: 38 to 45) of patients satisfied at least one of the composite criteria for CID. This is in contrast with 67% (95% CI 64 to 69) that had achieved an active joint count of zero. A third of CYP had no active joints, but did not achieve a score of zero on the PGA (33%). Rarely a child with active joints was scored at zero on the PGA (4%). In these few cases, CYP had only one active joint and appeared well on other disease variables (Table 24). Physicians and parents appeared to score differently with only 35% overlap in patients scoring zero on both the PGA and PGE (Figure 16.a). The JADAS and cJADAS criteria, which include a mixture of physician and parent-assessed measures, had a high degree of overlap (almost 100%) and both identified 38% of CYP as in CID at one year (Table 23, Figure 16.b.). Discrepancies between these two groups was driven by ESR, with patients (n=3) in CID only on the cJADAS with median 42mm/h ESR (IQR 34 to 65 mm/hr), compared with 6mm/h (IQR 2 to 11 mm/hr) for those in CID on both criteria (Table 24).

Fewer patients achieved CID on Wallace's preliminary criteria (25%, contains only physician-assessed components) compared with the JADAS criteria (38%, contains both physician and parent-assessed components). In accordance, there was only a 44% overlap in the patients identified in CID by these criteria (Figure 16.c). Where discordances existed between patients defined as in CID on the Wallace's preliminary criteria only or the JADAS10 only, large differences in the PGE (median 2.7cm and 0.0cm, respectively) were evident. However, patients in CID on the cJADAS had median PGA of 0.2cm, highlighting the requirement of an absolute cut-off of 0cm required for the Wallace's preliminary criteria. In addition, 4% of patients with systemic JIA in CID on the JADAS10 were recorded as having had active systemic features (Table 24). There were no differences in active joint count or ESR between these groups.

### Estimates of MDA across Criteria

At one year following presentation, 65% (95% CI: 62 to 68) of patients satisfied at least one of the three MDA criteria. The range in proportion of CYP achieving this state was smaller than using CID criteria, ranging from 48% on the cJADAS to 61% using the Magni-Manzoni criteria (Table 23). There was also greater overlap between MDA criteria than CID with 68% of CYP classified in MDA by all three criteria. The largest discrepancy was for the Magni-Manzoni criteria, which does not require use of the PGE score in oligoarticular JIA (Figure 16.d). In accordance, median PGE scores were higher in

patients in MDA only on the Magni-Manzoni criteria compared with the JADAS10 (2.9cm, IQR 2.0cm to 5.0cm vs. 0.2cm, IQR 0.0, 0.8) (Table 24).



a)



b)



c)

MDA
JADAS10

MDA
Magni-Manzoni

4.5%   5.5%   16%

68%

2.7%   3.3%

0.3%

MDA
cJADAS10

n=922
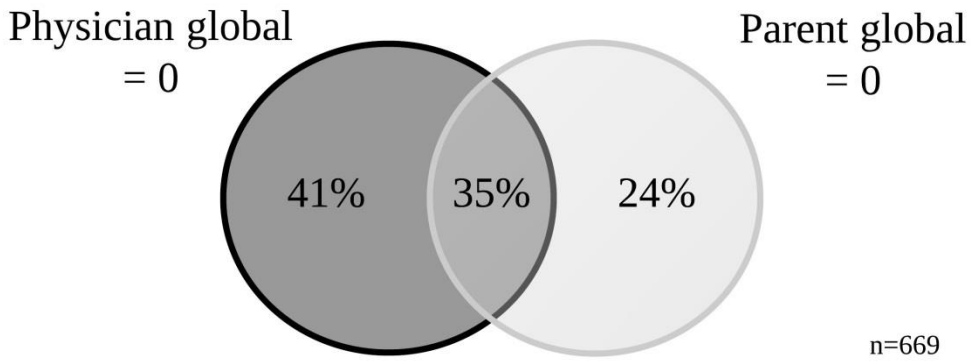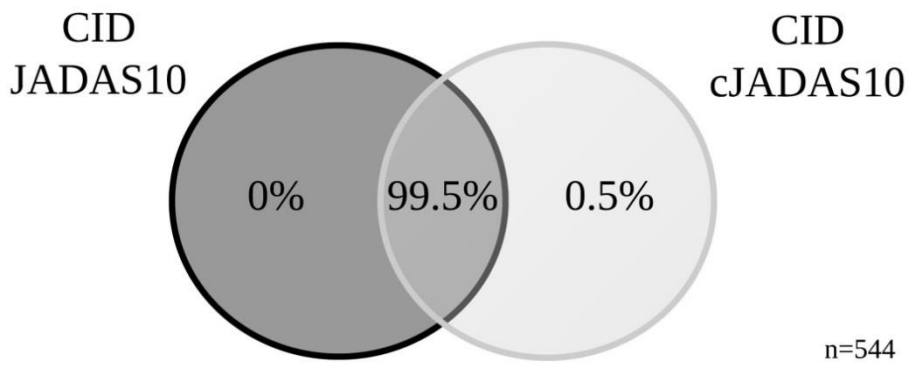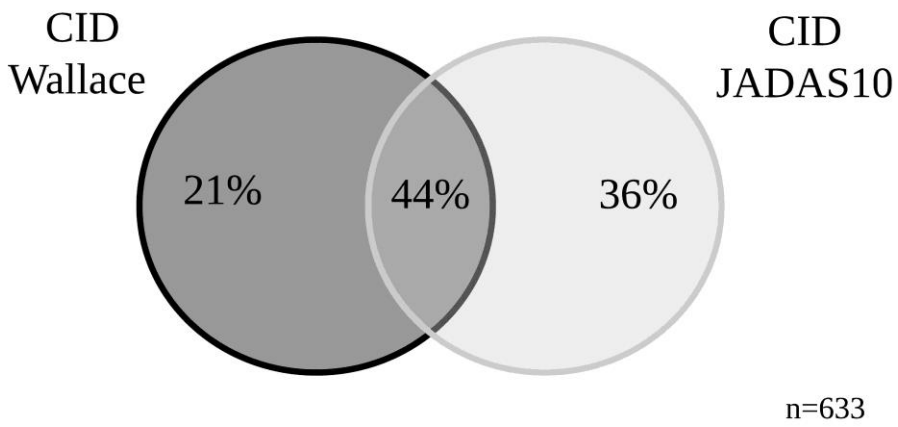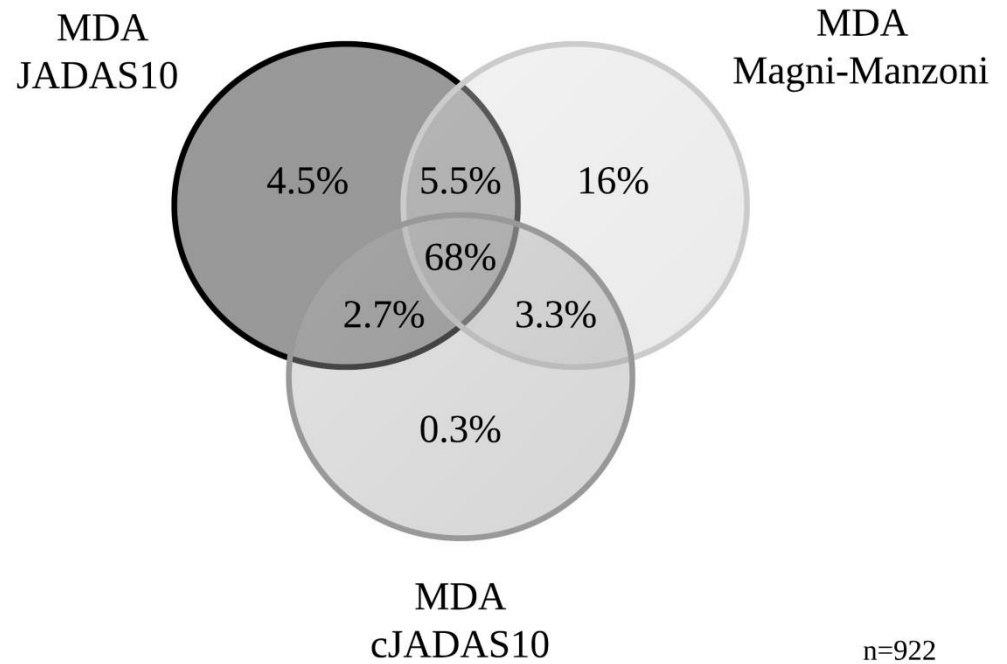
d)

**Figure 16. Percent patient overlap between outcome criteria: a) Zero on the PGA vs. PGE, b) CID JADAS10 vs. cJADAS10, c) CID Wallace's preliminary criteria vs. JADAS10 and d) MDA Magni-Manzoni, JADAS10 and cJADAS10.** For each figure, percentages are out of all CYP who satisfied at least one of the criteria displayed.

**Table 24.** Comparison of disease activity where CID/MDA criteria were discordant

| Discordant criteria | N | Component | | | | |
|---|---|---|---|---|---|---|
| | | Active joint count (median, IQR) | Physician global (cm) (median, IQR) | Parental global (cm) (median, IQR) | Percent with systemic features (%) | ESR (median, IQR) |
| **Zero active joints vs. zero on physician global** | | | | | | |
| Zero active joints only | 465 | 0 (0, 0) | 0.5 (0.2, 1.2) | 0.6 (0.1, 2.5) | 4 | 8 (3, 18) |
| Zero on physician global only | 54 | 1 (1, 1) | 0.0 (0.0, 0.0) | 0.5 (0.0, 2.1) | 1 | 7 (3, 16) |
| Zero on both | 474 | 0 (0, 0) | 0.0 (0.0, 0.0) | 0.1 (0.0, 0.8) | 2 | 7 (3, 16) |
| **Zero on physician vs. parental global** | | | | | | |
| Zero on physician global only | 274 | 0 (0, 0) | 0.0 (0.0, 0.0) | 0.8 (0.2, 2.2) | 2 | 3 (1, 7) |
| Zero on parental global only | 234 | 0 (0, 1) | 0.5 (0.2, 1.5) | 0.0 (0.0, 0.0) | 4 | 8 (4, 20) |
| Zero on both | 161 | 0 (0, 0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 2 | 7 (3, 17) |
| **CID Wallace's preliminary criteria vs. JADAS10** | | | | | | |
| CID only Wallace's preliminary criteria | 93 | 0 (0, 0) | 0.0 (0.0, 0.0) | 2.2 (1.4, 4.4) | 0 | 7 (3, 20) |
| CID only JADAS10 | 327 | 0 (0, 0) | 0.2 (0.1, 0.4) | 0.0 (0.0, 0.3) | 4 | 6 (3, 12) |
| CID on both | 213 | 0 (0, 0) | 0.0 (0.0, 0.0) | 0.1 (0.0, 0.3) | 0 | 6 (2, 11) |
| **CID JADAS10 vs. cJADAS10** | | | | | | |
| CID only on JADAS | 0 | - | - | - | - | - |
| CID only on cJADAS | 3 | 0 (0, 0) | 0.1 (0.0, 0.1) | 0.1 (0.0, 0.3) | 2 | 42 (34, 65) |
| CID on both | 541 | | | | 2 | 6 (2, 11) |
| **MDA Magni-Manzoni vs. JADAS10** | | | | | | |
| MDA Magni-Manzoni only | 149 | 0 (0, 0) | 0.4 (0.0, 1.5) | 2.9 (2.0, 5.0) | 4 | 12 (5, 35) |
| MDA JADAS10 only | 69 | 1 (1, 1) | 0.3 (0.0, 0.6) | 0.2 (0.0, 0.8) | 5 | 6 (3, 12) |
| MDA on both | 704 | 0 (0, 0) | 0.0 (0.0, 0.3) | 0.1 (0.0, 0.5) | 2 | 7 (3, 12) |

IQR: Interquartile range, ESR: Erythrocyte sedimentation rate, CID: Clinically inactive disease, MDA: Minimal disease activity, JADAS10: Juvenile Arthritis Disease

Activity Score using 10 joints.

### 6.2.5.3 The Frequency of CID and MDA in each ILAR Subtype

A similar pattern across outcome criteria was seen across all ILAR categories, with patients achieving no active joints more frequently than MDA, CID on JADAS and CID on Wallace's preliminary criteria, respectively (Figure 17). However, achievement of the most stringent composite criteria was achieved most frequently in the oligoarticular subtype (CID Wallace's preliminary criteria: 29%, CID JADAS10 43%). Patients with systemic JIA experienced large variation in their outcomes, achieving fewer of the criteria sets when more information on systemic features was taken into account. These CYP had high achievement of no active joints (78%), but only 14% achieved CID on Wallace's preliminary criteria (Figure 17; Supplementary Table 5).
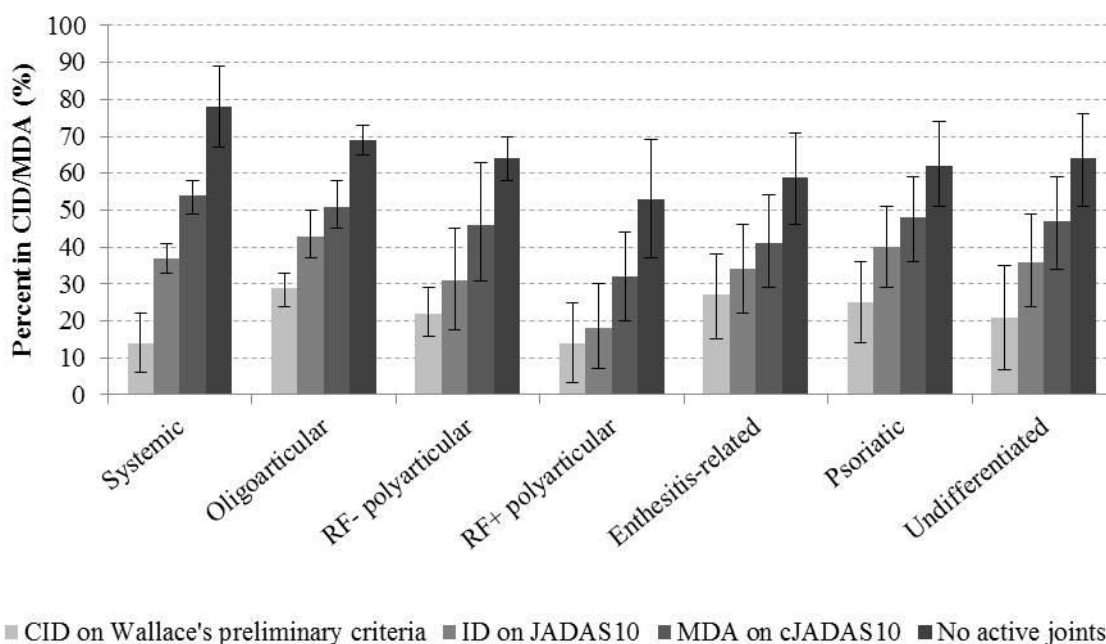


**Figure 17.** Percent of patients with JIA who had achieved CID and MDA states at one year following presentation.

### 6.2.6 Discussion

Since the success of treat-to-target approaches in RA [383,384], similar strategies in JIA have been considered [157,385-387]. However, many published and investigator-defined targets have been used across research [254,388,389]. The current study highlights that even published targets intended to capture the same construct identify different groups of CYP. Results from studies using different outcome criteria therefore cannot be compared directly. In

addition, if used as targets in clinical practice, utilising different targets may result in over- or under-treatment.

Achievement of CID and MDA varied greatly between criteria in this cohort. Broad achievement of CID was around 30% and MDA around 50%. This indicates a significant level of on-going disease symptoms at one year following initial presentation. Using Wallace's preliminary criteria, only 25% of CYP achieved CID. Higher estimates have been gained from other inception cohorts within similar time-frames in the literature, with estimates of 45% within one year [5] and 53% at 18 months [362]. These higher estimates are likely artefacts of measuring ever achievement in the former study and not including CYP with polyarticular JIA in the latter. Estimates of CID from the literature not using Wallace's preliminary criteria vary widely from 19% [257] to 60% [369].

Estimates of CID using newer criteria, including cut-offs on the JADAS [168] or cJADAS [186] have not yet been published from other inception cohorts. The current study found that the JADAS and cJADAS CID cut-offs have high overlap, capturing almost identical groups of CYP. Where discordant, CYP only in CID on the cJADAS had substantially higher ESR (42 mm/hr vs. 0 mm/hr). That so few CYP presented with low symptomatology but high inflammatory markers suggests a non-rheumatological cause of high ESR, such as recent infection. The cJADAS was designed to be more feasible in clinical practice compared with JADAS, since ESR is not required [198]. Since overlap between these criteria was excellent and complete data was available in 20% more patients in the three variable cJADAS, the current data supports the use of cJADAS in preference to JADAS when assessing CID. However, overlap between the JADAS and Wallace's preliminary criteria was poorer.

Lower overlap between the physician and parent global assessments, and between Wallace's preliminary criteria and the JADAS criteria, may reflect the different components included within each criteria and challenges the concept of what constitutes inactive or minimal disease in JIA. Unlike Wallace's preliminary criteria, the JADAS and cJADAS include a subjective parent (child)-assessed component (Table 21). Overlap between this and either JADAS set of criteria was only 44% (Figure 16). The minimally different median scores on the PGA for CYP in CID only on Wallace's preliminary criteria (0.0cm) versus only the JADAS10 (0.2cm) suggest that clinicians may not mark CYP at exactly zero, even on resolution of active disease. In this study, scores were recorded on paper and transcribed into the study database. With a move to online data capture and electronic medical records, this issue may resolve if relating to transcription errors, but

equally it may be that clinicians did not feel they could mark at exactly zero. These issues are resolved when using criteria such as the JADAS or cJADAS. Since CID on these numeric rating scales is defined as any score lower or equal to one, minimal scores above zero will be captured as part of the spectrum of CID. However, the substantial difference in the PGE (medians 2.2cm and 0.0cm, respectively) suggest a marked difference in global wellbeing for CYP identified as CID on the different criteria. The patient global assessment has been shown to be driven in large part by on-going pain [195,390]. A feature of JIA for a subset of CYP is the resolution of inflammation with persistent pain symptoms, which patients themselves have considered as active disease [391]. Whilst it is not possible to disentangle pain, related to inflammation or not, from other active disease symptoms using patient and parent global assessments, any symptom that patients themselves feel relate to their disease and require treatment via rheumatology should be treated as such. In concordance, applying criteria such as the JADAS and cJADAS which assess both inflammation and a patient's assessment of their disease may identify CYP with persistent chronic pain independent of joint inflammation, particularly in cases where scores are high despite the absence of active joints. These CYP could then be targeted for alternative pain management strategies, for example psychological support.

ILAR subtype-specific estimates provided some evidence that patients with the less common subtypes are less likely to achieve CID. This may be a result of higher PGA ratings for patients with extra-articular features, including exanthema and macrophage activation syndrome for systemic JIA. For the majority of criteria, oligoarticular JIA was the most favourable disease course with RF-positive polyarticular the least favourable, corroborating existing evidence [5,250,281,392]. Patients with systemic disease had the largest variation in outcome estimates (14% to 78%), which was largely driven by components of the individual composite criteria; when more information on systemic features was included, fewer CYP in this subtype achieved the outcome. This trend indicates that systemic features should be included when assessing CID or MDA in CYP with systemic JIA and highlights the importance of both physician and patient/parent reported global scores. Since no sets of criteria included in this analysis explicitly captured enthesitis or psoriasis, it remains to be seen whether the inclusion of criteria based on these features improves the measurement of CID in affected CYP.

The current study benefits from studying a large inception cohort of patients across all ILAR subtypes of JIA. It highlights the difference in disease states being targeted by clinicians and used as outcomes in research. Going forward, the introduction of composite measures and treatment targets into the clinical setting have the potential to streamline the

collection of clinical data, enabling comparisons from one visit to the next and between different centres. Further work is indicated to establish the feasibility, acceptability and utility of composite scores and treatment targets in clinical practice as well as in the context of clinical trials to improve future data capture and completeness. This study also provides an update on the frequency of CID and remission in a contemporary JIA cohort. This information is very important in the clinical setting, helping clinicians to realistically manage patient expectations at presentation. As the primary outcome was overlap between the published definitions which is unlikely to change over time, multiple time points were not assessed. A previous study in this cohort, however, assessed achievement of CID on the cJADAS71 across CYP with JIA who initially presented to paediatric rheumatology between 2001 and 2011. They reported no significant increase in CID achievement for CYP presenting in later years, despite a wider variety of biologic availability and a culture of more aggressive treatment strategies [387,393].

Limitations of the current study include that CID criteria were applied to ILAR categories in which they are not validated: namely systemic, enthesitis-related and psoriatic JIA. However, the majority of previous studies have applied CID criteria in their entire cohort including all categories [30,273,275,276,394]. To therefore assess the same disease state as applied in existing literature and allow comparisons across all outcomes, the criteria were applied to all JIA subtypes. As a consequence, current estimates may overestimate the frequency of CID in CYP with persistent systemic manifestations, enthesitis or psoriasis but no active joint inflammation. Since these features are relatively rare, estimates across the entire cohort were likely only marginally affected by their inclusion and these features are at least partially reflected in physician and parental global scores. ILAR subtype specific definitions of CID may be of value in the future.

In this study, all items were captured as part of routine care and not specifically within the setting of a clinical trial or study, and many of the criteria included were not designed for a busy clinical setting [395]. The capture of these items in routine clinical care of JIA vary greatly between clinical settings and composite measures of disease activity were not routinely collected in UK practice during the time of data capture in this study. This is reflected in part by the amounts of missing data, a common observation in "real-world" research studies. The volume of missing data was particularly high for composite measures, where multiple elements were often not collected routinely. We account for these missing data using a number of assumptions and multiple imputation. Estimates using complete case analyses were substantially lower than after imputation, partly due to CYP with active disease being easier to classify in the complete case analysis (see online

supplementary text). The majority of data missing were for laboratory measures, with only 20% of CYP having ESR recorded at one year, reflecting that CYP who are well may not have blood tests. Fantini and others reported also that patients lost to follow-up had greater remission rates than those present at follow-up [250]. These trends likely biased complete case estimates towards a greater proportion of CYP with on-going disease activity.

The frequency of remission according to the 2011 ACR preliminary criteria [185] could not be calculated in the current study. This set of criteria requires information on morning stiffness, which is notoriously difficult to determine in young CYP and which was not collected as part of CAPS. International consensus should be reached about a minimal core data set for both observational and interventional research. This would not only aid monitoring of the JIA disease course and response to therapies, but also aid comparability between clinical research studies. Where feasible, future work should compare the frequency of achieving the CID on the ACR 2011 preliminary criteria with the states highlighted in the current study.

Finally, this study highlights that published definitions of CID and MDA identify distinctly different groups of CYP. Whilst the cJADAS10 cut-offs are more feasible to apply in clinical practice and appear to capture a greater picture of active JIA compared with Wallace's preliminary criteria, this study does not provide data to support which measure is optimal in terms of long-term outcomes. Future studies should compare long-term outcomes following early achievement of these measures to provide evidence for a potential aim for treat-to-target approaches. Currently, there are no recommendations for optimal treat-to-target strategies and as such, these strategies are not common practice.

### 6.2.7   Conclusion

In a large inception cohort, a large proportion of patients with JIA had evidence of persistent disease activity one year following first presentation to paediatric or adolescent rheumatology. However, the estimates of these disease states differed widely based on which set of criteria was applied, many of which were not disease subtype-specific. These differences highlight that the same child could be classified as 'in CID' or having active disease at the same time point between clinicians or hospitals.  Future work needs to explore which treatment target predicts better long-term prognoses in JIA.

### 6.2.8   Acknowledgements

### 6.2.9   Competing Interests

The authors declare no conflicts of interest.

### 6.2.10  Supplementary Materials

#### 6.2.10.1    Methods for Handling Missing Data

Outcome frequencies were assessed using complete case analysis in a secondary analysis. This included CYP for whom a complete dataset was not available but the child could still be classified as 'not in CID/MDA' if one available component excluded that possibility. For example, a child scoring 2cm on the PGA could not be in CID on any set of criteria. This child was classified as 'not in CID', even if other missing data existed.

All imputation models were completed under the same random number seed (5879). Variables entered into the imputation models included hospital, gender, age, disease duration at presentation, active joint count, PGA, PGE, ESR, CRP, CHAQ, ILAR subtype and non-steroid anti-inflammatory drug, steroids or disease-modifying anti-rheumatic drug prescription (yes/no). Continuous variables were transformed to normal distributions before imputation [325], after which they were converted back to their original forms. Composite criteria estimates were calculated using individual components following imputations.

**Supplementary Table 5.** The frequency of CID/MDA in each ILAR category of all patients using multiple imputation assuming data MNAR

| ID criteria | Percent of patients in CID/MDA at year one of follow-up using Multiple Imputation assuming data MNAR (%) (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Systemic (n=96) | Oligo (n=707) | RF- Poly (n=292) | RF+ Poly (n=49) | ERA (n=77) | PsA (n=97) | Undiff. (n=97) |
| **Single criteria for CID** | | | | | | | |
| Active joint count = 0 | 78 (67, 89) | 69 (65, 73) | 64 (58, 70) | 53 (37, 69) | 59 (46, 71) | 62 (51, 74) | 64, 51, 76) |
| Physician global assessment = 0 | 32 (21, 43) | 40 (35, 45) | 30 (24, 36) | 18 (5.6, 31) | 36 (24, 47) | 39 (28, 51) | 36 (21, 51) |
| Parental global evaluation= 0 | 29 (19, 40) | 32 (28, 36) | 19 (14, 25) | 14 (2.7, 26) | 25 (14, 36) | 25 (14, 37) | 30 (19, 42) |
| **Composite criteria for CID** | | | | | | | |
| Wallace's preliminary criteria for CID | 19 (8.8, 28) | 34 (30, 38) | 25 (19, 30) | 17 (5.1, 29) | 31 (19, 43) | 32 (21, 43) | 27 (15, 40) |
| CID using JADAS10 | 37 (26, 49) | 43, 39, 47) | 31 (25, 38) | 18 (4.6, 32) | 34 (22, 46) | 40 (29, 51) | 36 (24, 49) |
| CID using JADAS71 | 37 (26, 49) | 43 (39, 47) | 31 (25, 38) | 18 (4.6, 32) | 34 (22, 46) | 40 (29, 51) | 36 (24, 49) |
| CID using cJADAS10 | 38 (26, 49) | 43 (39, 48) | 32 (26, 38) | 18 (4.6, 32) | 34 (22, 46) | 40 (29, 51) | 36 (24, 49) |
| **Composite criteria for MDA** | | | | | | | |
| MDA using JADAS10 | 53 (42, 64) | 52 (48, 57) | 57 (50, 63) | 44 (28, 61) | 46 (32, 60) | 51 (40, 63) | 53 (40, 66) |
| MDA using JADAS71 | 53 (42, 64) | 52 (48, 57) | 57 (50, 63) | 44 (28, 61) | 46 (32, 60) | 51 (40, 63) | 53 (40, 66) |
| MDA using cJADAS10 | 54 (42, 66) | 51 (46, 55) | 46 (40, 53) | 32 (17, 49) | 41 (29, 54) | 48 (36, 59) | 47 (34, 59) |
| MDA (Magni-Manzoni) | 59 (49, 70) | 69 (65, 73) | 52 (46, 59) | 38 (22, 53) | 53 (40, 66) | 59 (47, 71) | 59 (46, 71) |

MNAR: missing not at random; Oligo: oligoarticular JIA; RF- Poly: RF negative polyarticular JIA, RF+ poly: RF positive polyarticular JIA, ERA: Enthesitis-related JIA, PsA: Psoriatic JIA, Undiff. Undifferentiated JIA. Pers: Persistent; Ext: Extended; CID: Clinically inactive disease; MDA: Minimal disease activity; JADAS: Juvenile arthritis disease activity score in 10 (JADAS10) and 71 (JADAS71) joints and excluding ESR (cJADAS10).

**Supplementary Table 6.** The frequency of CID/MDA in each ILAR category using multiple imputation assuming data MNAR for cohort 1*

| ID criteria | Percent of patients in CID/MDA at year one of follow-up using Multiple Imputation assuming data MNAR (%) (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Systemic (n=31) | Oligo (n=265) | RF- Poly (n=109) | RF+ Poly (n=20) | ERA (n=36) | PsA (n=38) | Undiff. (n=28) |
| **Single criteria for CID** | | | | | | | |
| Active joint count = 0 | 80 (64, 95) | 64 (58, 70) | 62 (52, 71) | 40 (16, 64) | 57 (40, 75) | 61 (44, 78) | 61, (39, 84) |
| Physician global assessment = 0 | 13 (0, 27) | 36 (30, 42) | 25 (16, 34) | 17 (0, 35) | 30 (14, 46) | 37 (20, 54) | 31 (9, 52) |
| Parental global evaluation= 0 | 18 (0, 37) | 30 (24, 35) | 15 (7, 23) | 17 (0, 39) | 31 (13, 48) | 25 (9, 42) | 41 (18, 63) |
| **Composite criteria for CID** | | | | | | | |
| Wallace's preliminary criteria for CID | 7.4 (0, 18) | 30 (24, 36) | 21 (12, 29) | 15 (0, 32) | 27 (11, 44) | 34 (17, 50) | 27 (7, 46) |
| CID using JADAS10 | 25 (8, 42) | 43 (37, 50) | 31 (21, 40) | 13 (0, 32) | 33 (16, 50) | 41 (23, 59) | 43 (20, 66) |
| CID using JADAS71 | 25 (8, 42) | 43 (37, 50) | 31 (21, 40) | 13 (0, 32) | 33 (16, 50) | 41 (23, 59) | 43 (20, 66) |
| CID using cJADAS10 | 25 (8, 42) | 43 (37, 50) | 31 (21, 40) | 13 (0, 32) | 33 (16, 50) | 41 (23, 59) | 43 (20, 66) |
| **Composite criteria for MDA** | | | | | | | |
| MDA using JADAS10 | 43 (23, 63) | 47 (42, 53) | 56 (46, 66) | 33 (6, 60) | 45 (26, 63) | 48 (29, 67) | 61 (38, 83) |
| MDA using JADAS71 | 43 (23, 63) | 47 (42, 53) | 56 (46, 66) | 33 (6, 60) | 45 (26, 63) | 48 (29, 67) | 61 (38, 83) |
| MDA using cJADAS10 | 49 (29, 68) | 52 (45, 58) | 46 (36, 56) | 17 (0, 39) | 40 (22, 57) | 48 (28, 67) | 56 (33, 79) |
| MDA (Magni-Manzoni) | 53 (33, 73) | 66 (60, 72) | 54 (44, 63) | 31 (5, 56) | 49 (32, 66) | 61 (43, 79) | 61 (38, 84) |

*Cohort 1: First presentation to paediatric rheumatology between 2001 and 2006. MNAR: missing not at random; Oligo: oligoarticular JIA; RF- Poly: RF negative polyarticular JIA, RF+ poly: RF positive polyarticular JIA, ERA: Enthesitis-related JIA, PsA: Psoriatic JIA, Undiff. Undifferentiated JIA. Pers: Persistent; Ext: Extended; CID: Clinically inactive disease; MDA: Minimal disease activity; JADAS: Juvenile arthritis disease activity score in 10 (JADAS10) and 71 (JADAS71) joints and excluding ESR (cJADAS10).

**Supplementary Table 7.** The frequency of CID/MDA in each ILAR category using multiple imputation assuming data MNAR for cohort 2*

| ID criteria | Percent of patients in CID/MDA at year one of follow-up using Multiple Imputation assuming data MNAR (%) (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Systemic (n=65) | Oligo (n=442) | RF-Poly (n=183) | Poly RF+ (n=29) | ERA (n=41) | PsA (n=59) | Undiff. (n=69) |
| **Single criteria for CID** | | | | | | | |
| Active joint count = 0 | 77 (64, 90) | 70 (65, 75) | 64 (57, 72) | 64 (42, 85) | 60 (42, 79) | 61 (47, 75) | 62 (44, 81) |
| Physician global assessment = 0 | 44 (29, 59) | 42 (37, 47) | 34 (26, 42) | 24 (1, 47) | 42 (23, 61) | 43 (27, 59) | 42 (24, 61) |
| Parental global evaluation= 0 | 37 (21, 52) | 34 (29, 40) | 22 (14, 30) | 16 (0, 33) | 16 (0, 33) | 24 (11, 38) | 24 (12, 37) |
| **Composite criteria for CID** | | | | | | | |
| Wallace's preliminary criteria for CID | 24 (11, 37) | 34 (28, 39) | 27 (20, 34) | 19 (0, 37) | 34 (16, 53) | 31 (16, 47) | 28 (12, 44) |
| CID using JADAS10 | 45 (31, 60) | 44 (39, 50) | 34 (26, 42) | 24 (5, 43) | 37 (18, 55) | 40 (24, 56) | 34 (17, 51) |
| CID using JADAS71 | 45 (31, 60) | 44 (39, 50) | 34 (26, 42) | 24 (5, 43) | 37 (18, 55) | 40 (24, 56) | 34 (17, 51) |
| CID using cJADAS10 | 47 (31, 62) | 45 (39, 50) | 34 (26, 42) | 42 (5, 43) | 37 (18, 55) | 40 (24, 56) | 34 (17, 51) |
| **Composite criteria for MDA** | | | | | | | |
| MDA using JADAS10 | 60 (43, 76) | 52 (47, 57) | 62 (54, 69) | 56 (35, 77) | 50 (30, 70) | 55 (40, 70) | 53 (36, 71) |
| MDA using JADAS71 | 60 (43, 76) | 52 (47, 57) | 62 (54, 69) | 56 (35, 77) | 50 (30, 70) | 55 (40, 70) | 53 (36, 71) |
| MDA using cJADAS10 | 59 (44, 74) | 54 (48, 59) | 49 (40, 57) | 45 (24, 66) | 46 (27, 65) | 50 (34, 65) | 45 (28, 63) |
| MDA (Magni-Manzoni) | 64 (50, 79) | 72 (66, 80) | 55 (47, 63) | 46 (24, 69) | 57 (40, 75) | 59 (45, 73) | 57 (38, 76) |

*Cohort 2: First presentation to paediatric rheumatology between 2007 and 2013. MNAR: missing not at random; Oligo: Oligoarthritis; RF- Poly: RF-negative polyarthritis, RF+ poly: RF positive polyarthritis, ERA: Enthesitis-related JIA, PsA: Psoriatic JIA, Undiff. Undifferentiated JIA. Pers: Persistent; Ext: Extended; CID: Clinically inactive disease; MDA: Minimal disease activity; JADAS: Juvenile arthritis disease activity score in 10 (JADAS10) and 71 (JADAS71) joints and excluding ESR (cJADAS10).

**Supplementary Table 8.** The frequency of CID/MDA in each ILAR category using Complete Case analysis

| Outcome | Percent of patients in CID/MDA at year one of follow-up using Complete Case analysis (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No. missing (%) | Systemic (max n=90) | Oligo (max* n=663) | RF- Poly (max n=282) | RF+ Poly (max n=47) | ERA (max n=72) | PsA (max n=94) | Undiff. (max n=76) |
| **Single criteria for CID** | | | | | | | | |
| Discharge from rheumatology due to low disease activity | 66 (4.7) | 1 (1.1) | 9 (1.4) | 2 (0.7) | 0 (0.0) | 1 (1.4) | 1 (1.1) | 2 (2.6) |
| Active joint count = 0 | 415 (29) | 50 (55) | 253 (38) | 102 (36) | 11 (22) | 22 (30) | 32 (34) | 10 (13) |
| Physician global assessment = 0 | 596 (42) | 15 (28) | 145 (35) | 57 (30) | 5 (15) | 17 (33) | 21 (36) | 5 (25) |
| Parental global evaluation = 0 | 491 (35) | 16 (26) | 134 (29) | 31 (15) | 4 (12) | 8 (16) | 11 (17) | 11 (24) |
| **Composite criteria for CID** | | | | | | | | |
| Wallace's preliminary criteria for CID | 514 (39) | 2 (3.2) | 11 (3.0) | 16 (7.8) | 4 (9.8) | 2 (4.2) | 1 (1.6) | 0 (0.0) |
| CID using JADAS10 | 638 (48) | 5 (9.8) | 13 (4.3) | 10 (5.8) | 0 (0.0) | 1 (2.4) | 5 (9.4) | 1 (3.2) |
| CID using JADAS71 | 638 (48) | 5 (9.8) | 13 (4.3) | 10 (5.8) | 0 (0.0) | 1 (2.4) | 5 (9.4) | 1 (3.2) |
| ID using cJADAS10 | 708 (53) | 16 (39) | 130 (42) | 46 (32) | 3 (13) | 12 (30) | 19 (45) | 6 (40) |
| **Composite criteria for MDA** | | | | | | | | |
| MDA using JADAS10 | 887 | 7 (18) | 23 (9.7) | 25 (20) | 3 (13) | 3 (8.6) | 7 (16) | 2 (10) |
| MDA using JADAS71 | 887 | 7 (18) | 23 (9.7) | 25 (20) | 3 (13) | 3 (8.6) | 7 (16) | 2 (10) |
| MDA using cJADAS10 | 602 | 3 (13) | 7 (18) | 23 (9.7) | 25 (20) | 3 (8.6) | 7 (16) | 2 (10) |
| MDA criteria (Magni-Manzoni) | 545 | 25 (46) | 271 (62) | 82 (42) | 7 (22) | 24 (44) | 34 (52) | 12 (41) |

*The sample sizes represent the total number of CYP with these subtypes. However, missing data may have been evident so that the total number will not have been categorised by each set of CID criteria. Oligo: oligoarthritis; RF- poly: Rheumatoid factor negative polyarthritis; RF+ poly: Rheumatoid factor positive polyarthritis; ERA: Enthesitis-related arthritis; PsA: Psoriatic arthritis; Undiff: Undifferentiated arthritis; CID: Clinically inactive disease; MDA: Minimal disease activity; JADAS: Juvenile arthritis disease activity score using 10 (JADAS10) and 71 (JADAS71) joints and excluding ESR (cJADAS10).

## 6.3 Long term Outcomes Following Achievement of Clinically Inactive Disease in Juvenile Idiopathic Arthritis: the Importance of Definition

**Published in Arthritis and Rheumatology**

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**Word count (excluding references):** 3188

**Key words:** Juvenile idiopathic arthritis, Inactive disease, Minimal disease activity, Treatment target, Health outcomes

### 6.3.2   Competing Interests

The authors declare no conflicts of interest.

### 6.3.3   Abstract

**Background:** Potential targets for treat-to-target strategies in JIA are minimal disease activity (MDA) and clinically inactive disease (CID). Short and long-term outcomes following achievement of MDA and CID on the cJADAS10 and CID on Wallace's preliminary criteria were compared.

**Methods:** Children and young people (CYP) recruited to the Childhood Arthritis Prospective Study, a UK multicentre inception cohort, were selected if recruited prior to January 2011 and diagnosed with oligoarthritis or rheumatoid factor negative or positive polyarthritis.

At one year following diagnosis, CYP were assessed for MDA on the cJADAS10 and CID on both Wallace's preliminary criteria and the cJADAS10. Associations were tested between these disease states and i) functional ability, ii) absence of limited joints, iii) psychosocial health and iv) pain at one year and annually to five years.

**Results:** Of 832 CYP, 70% were female and the majority had oligoarthritis (68%). At one year, 21% had achieved CID according to both definitions, 7% on Wallace's preliminary criteria only, 16% on cJADAS10 only and 56% on neither. Only 10% of CYP in the entire cohort achieved MDA without also having CID.

Achieving either early CID state was associated with greater absence of limited joints. However, only CID on cJADAS10 was associated with improved functional ability and psychosocial health. Achieving CID was superior to MDA in terms of short and long-term pain and the absence of limited joints.

**Conclusion:** CID on the cJADAS10 may be a preferable treatment target to CID on Wallace's preliminary criteria in terms of both feasibility of application and long-term outcomes.

### 6.3.4  Introduction

Despite the licencing of biologic therapies for juvenile idiopathic arthritis (JIA) [118], and increasingly aggressive treatment strategies [396], a recent systematic review estimates that the burden of disease in JIA remains high, with fewer than 50% of patients achieving remission after a decade of disease [397]. Following the success of treat-to-target approaches in adult rheumatology [383,384], a similar approach in JIA may yield better disease outcomes [152]. However, it is less clear what the target should be. One target for children and young people (CYP) with JIA is clinically inactive disease (CID), a state where no evidence of disease activity is apparent [237]. Whilst a state of CID, and ultimately disease remission, would be ideal, it may not be feasible in all CYP due to the nature of their JIA disease activity. In addition, the acceptability of treatment required for such a state may not be acceptable when weighted against additional risks of adverse events and the cost of additional therapies. An alternative target could therefore be minimal disease activity (MDA), a state which would include CYP with CID but also those with low but persistent disease activity [252].

Defining disease states such as CID in clinical practice can be challenging and currently rely on composite criteria [397,398]. Multiple such definitions have been proposed, including CID using Wallace's preliminary criteria [237], the ACR 2011 CID criteria [185] and scoring below certain cut-offs on the Juvenile Arthritis Disease Activity Score (JADAS) [240] or clinical (c)JADAS [186]. Wallace's preliminary criteria includes five components, observed or measured by a physician, which must all be absent or in the normal range, but do not include an assessment by the patient or their proxy [237]. In contrast, the JADAS and cJADAS include fewer overall components, meaning they may be easier to complete in a routine clinical setting, but do include a patient or proxy subjective assessment of patient wellbeing [186,240]. Although Wallace's preliminary criteria and low score cut-offs on the JADAS or cJADAS are intended to identify similar disease constructs, a recent analysis has shown that these definitions will classify different groups of CYP as having CID, which may be driven by their different components [398]. It is currently unclear which definition, if any, should be applied in the clinical setting as a treatment target but the choice may be influenced by how achievement of CID according to each definition relates to later disease outcomes. It is also unclear whether applying increasingly aggressive treatment strategies to achieve CID beyond MDA is favourable in terms of long-term outcomes.

The aims of this study were therefore to (1) describe the impact of early achievement of CID on functional ability, joint limitations and psychosocial health over the first five years following initial presentation to paediatric rheumatology, (2) assess whether the applied definition of CID at one year is associated with different long term outcomes and (3) assess whether achieving CID is beneficial beyond MDA in terms of pain in addition to these outcomes according to the cJADAS10.

### 6.3.5  Patients and Methods

#### 6.3.5.1 Study Population

This analysis included CYP recruited to the Childhood Arthritis Prospective Study (CAPS), a prospective inception cohort recruiting from eight UK paediatric and adolescent rheumatology centres since 2001. Details of this cohort have been described previously [382]. CAPS was approved by the Northwest Multicentre Research Ethics Committee and written informed consent from guardians (and where appropriate, assent or consent from participants) was obtained.

For this study, CYP were included if they had a physician's diagnosis of JIA (oligoarticular and either rheumatoid factor (RF) negative or positive polyarticular categories) and had been recruited to CAPS prior to 1st January 2011, to allow for at least five years of follow-up. CYP were included in each analysis if outcome data were available for at least one of the time points studied. Those with no returned study forms after initial presentation were excluded.

#### 6.3.5.2    Data Collection

CAPS data were collected from the medical case notes at first presentation to paediatric rheumatology (baseline date) and annually thereafter for 5 years using a pre-defined study proforma. These include demographic and disease features, ILAR category as recorded by the treating physician in the case notes, and any anti-rheumatic treatments.  Collection of components of the CID/MDA criteria has been described previously [398].

At each follow-up visit, proxies (or the CYP themselves where possible if >11 years) were asked to complete a series of patient reported outcome measures, including the Childhood Health Assessment questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) [188]. The CHAQ score totals 24 and is divided so that final scores range from zero to three, with higher scores denoting poorer functional ability. It is known to have a flooring effect, whereby scores tend to cluster at the 'good functional ability' section of the scale [188].  The CHQ is a generic health-related quality of life (HRQoL) measure designed for proxy

completion for paediatric patients over the age of five. It is comprised of 15 subscales, 10 of which can be aggregated to gain a psychosocial summary score. This summary score ranges from 0 to 100, with higher scores denoting better HRQoL [399]. Scores below 30 are considered at least two standard deviations below population averages [400]. Patients/proxies also completed a 100mm pain VAS.

### 6.3.5.3 States of CID and MDA

Using data from one year following initial presentation, CYP were categorised regarding their CID status on Wallace's preliminary criteria [237] and the cJADAS10 [186]. CYP were therefore classed into the following states: i) CID on both criteria sets, ii) CID Wallace's preliminary criteria only, iii) CID cJADAS10 only, iv) No CID. CYP were also classified as to whether they fulfilled: i) CID on the cJADAS10 ii) MDA but not CID on the cJADAS10 (Table 25).

**Table 25.** Definitions of CID and MDA applied to the CAPS cohort

| Definition | Components | | | | | | How to calculate |
| | AJC | PGA | PGE | ESR/CRP | Uveitis | Systemic features in sJIA | |
|---|---|---|---|---|---|---|---|
| CID Wallace's preliminary criteria [237] | ✓ | ✓ | | ✓ | ✓ | ✓ | Zero or normal across all components |
| CID cJADAS10 [186] | ✓ | ✓ | ✓ | | | | Total score ≤1 |
| MDA cJADAS10 [186] | ✓ | ✓ | ✓ | | | | Oligoarticular course JIA score ≤1.5 |
| | | | | | | | Polyarticular course JIA score ≤2.5 |

CID: Clinically inactive disease, MDA: Minimal disease activity, cJADAS10: clinical Juvenile Arthritis Disease Activity Score in 10 joints, AJC: Active joint count, PGA: Physician's global assessment, PGE: Parental global evaluation, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, sJIA: systemic JIA.

### 6.3.5.4 Outcome Assessment

The following outcomes were selected: functional ability on the CHAQ, no limited joints, psychosocial health on the CHQ and pain. These outcomes were selected to avoid circular reasoning. For example, the cJADAS10 includes the PGE and Wallace's preliminary criteria do not. It would therefore be expected that CID on the cJADAS10 would be more strongly associated with better longitudinal PGE than CID on Wallace's preliminary criteria. To avoid this circular reasoning, all outcomes selected for the current study must not have formed one of the components of either CID/MDA criteria set. All outcomes were assessed annually from baseline to five years following initial presentation to paediatric rheumatology.

### 6.3.5.5 Statistical Analysis

#### Associations between CID/MDA and Short and Long-term Outcomes

Firstly, associations were tested between one year CID/MDA states cross-sectionally with the outcomes at one year. Secondly, associations between these one year states and outcomes annually from one to five years following initial presentation were analysed via multilevel, multivariable regression analyses. All CYP with outcomes available on at least one time point were included. Depending on the outcome, the following regression analyses were applied: logistic (no limited joints versus any limited joints, CHQ psychosocial<30 versus CHQ psychosocial ≥30) and linear (CHQ psychosocial, pain) regressions. The known flooring effect of the CHAQ, whereby scores cluster at the 'high functional ability' end of the scale [188] prompted its analysis using zero-inflated negative binomial regression models. These models incorporate the excessive zero counts by firstly generating odds ratios for having a score of zero versus not. Secondly, they produce risk ratios for increasing counts along the CHAQ scale among those subjects who have not scored 0. To analyse the CHAQ in this way, each value must be an integer. CHAQ scores were therefore multiplied by eight to yield their original score out of 24 points to allow its analysis as a count variable. Because one component of the cJADAS10 criteria set, the parental global assessment of wellbeing, has been reported to be driven by pain [195,390,401], pain was only used as an outcome when analysing associations between early CID versus MDA on the cJADAS10.

Data were analysed following multiple imputation under assumptions detailed in previous work [398] for CID/MDA states and under the assumption of data 'missing at random' for outcome data except CHQ psychosocial scores. Twenty imputed datasets were generated

in STATA14 and estimates from individual models pooled using Rubin's Rules, where both within and across-imputation variances are accounted for [333]. CHQ psychosocial scores were not imputed due to the likely unmeasured confounders that would inform these data.

Random effects were afforded at the patient level for longitudinal models. The zero-inflated longitudinal models instead incorporated robust clusters at the patient level. Multivariable models adjusted for hospital, age, symptom duration and year of presentation, gender and ILAR category with models at one year also adjusting for respective outcome at baseline. Covariate multicollinearity was assessed via Spearman's correlations and zero-inflated negative binomial models were deemed preferable to Poisson models if dispersion parameter 95% confidence intervals did not contain zero. All analyses were completed in STATA14 (Stata Corp, College Station, TX, USA).

### 6.3.6 Results

#### 6.3.6.1 Patient Cohort

A total of 1106 patients had been recruited to CAPS by the 1$^{st}$ January 2011. Of these, 274 were excluded (60 diagnosed with a non-JIA condition, 209 did not have oligoarticular or polyarticular JIA and five had no returned study forms). This left 832 patients for the current analyses, including 649 with available data on the CHQ psychosocial score at any time point (n=601 from one year onwards). By the end of the five year follow-up, 510 (61%) CYP remained under paediatric rheumatology care and had not been lost-to-follow-up or discharged (Supplementary Figure 1). The numbers of CYP with available data for each outcome across time points are described in Supplementary Table 9.

Within the cohort, median age at initial presentation to paediatric rheumatology was seven years (IQR 3 to 11) and median symptom duration at presentation was six months (IQR 3 to 11). Seventy percent of the cohort were female with 68%, 27% and 5% diagnosed with oligoarticular, RF-negative polyarticular and RF-positive polyarticular JIA, respectively (Table 26).

**Table 26.** Baseline characteristics of the patient cohort

| Characteristic | No. (%) patients with available baseline data | Median (IQR) or N (%) | No. (%) patients with available data at one year | Median (IQR) or N (%) |
|---|---|---|---|---|
| Female | 832 (100) | 586 (70) | | |
| White or Caucasian | 832 (100) | 752 (90) | | |
| Age at onset (years) | 827 (99) | 5.9 (2.4, 9.9) | | |
| Age at first presentation (years) | 832 (100) | 6.9 (3.1, 11) | | |
| Symptom duration at diagnosis (months) | 827 (99) | 5.5 (2.9, 11) | | |
| **ILAR category:** | | | | |
| Oligoarticular | 832 (100) | 563 (68) | | |
| RF- Polyarticular | | 231 (27) | | |
| RF+ Polyarticular | | 38 (5) | | |
| **Disease characteristics:** | | | | |
| Active joint count (/78) | 784 (94) | 2 (1, 5) | 689 (83) | 0 (0, 1) |
| Limited joint count (/78) | 784 (94) | 1 (1, 3) | 677 (81) | 0 (0, 1) |
| No limited joints | 784 (94) | 161 (21) | 677 (81) | 391 (58) |
| PGA (cm) | 630 (76) | 2.8 (1.5, 5.0) | 576 (69) | 0.4 (0.0, 1.8) |
| PGE (cm) | 546 (66) | 2.1 (0.5, 5.0) | 587 (71) | 0.6 (0.0, 2.5) |
| ESR (mm/hr) | 517 (62) | 16 (6, 40) | 194 (32) | 8 (4, 17) |
| CRP (mg/L) | 474 (57) | 7 (4, 19) | 173 (21) | 4 (3, 7) |
| Uveitis | 644 (77) | 27 (4.2) | 673 (81) | 30 (4.5) |
| CHAQ | 557 (67) | 0.8 (0.1, 1.4) | 573 (69) | 0.3 (0, 0.9) |
| Pain (mm) | 552 (66) | 30 (8, 58) | 572 (69) | 8 (1, 33) |
| CHQ | 281 (34) | 50 (39, 55) | 343 (41) | 52 (43, 58) |
| CHQ≤30 | 281 (34) | 32 (11) | 343 (41) | 23 (6.7) |

ILAR: International League of Associations for Rheumatology, RF: Rheumatoid factor, PGA: Physician's global assessment of disease activity, PGE: Proxy global assessment of wellbeing, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, CHAQ: Childhood Health Assessment Questionnaire, CHQ: Child Health Questionnaire, IQR: Interquartile range, CI: Confidence interval.

### *6.3.6.2 Frequency of Patients in CID and MDA at One Year*

At one year following initial presentation, the majority of patients had not achieved CID (56%). Twenty one percent had achieved both CID states, with an additional 23% having only achieved one state of CID: 16% only on the cJADAS and 7% only on Wallace's preliminary criteria. On the cJADAS10, 48% of patients had achieved MDA. Of these patients, 79% had also achieved CID (38% of the entire cohort).

### 6.3.6.3 Association between Early Achievement of CID and Outcomes Measured at One Year

All estimates from complete case analyses were similar to those following multiple imputation (Supplementary Table 10 & Supplementary Table 11). The following results relate to imputed data, except for CHQ psychosocial scores. All models met the tested assumptions.

At one year, achievement of any state of CID was associated with significantly increased odds of no limited joints at one year (Wallace only: OR 7.5 (95% CI 2.9 to 19.2), cJADAS only: OR 3.9 (95% CI 2.5 to 6.3), both CID states: OR 9.3 (95% CI 4.9 to 17.7)). However, CYP who had achieved CID only on Wallace's preliminary criteria but not cJADAS had no better CHQ psychosocial scores or CHAQ scores than those with active disease at one year. In contrast, those who had achieved CID on at least the cJADAS10 scored at least five points better on the CHQ psychosocial (cJADAS10 only: coefficient 5.3 (95% CI 0.5 to 10.1), both CID: coefficient 5.5 (95% CI 1.5 to 9.4)) than CYP with active disease. These CYP also had at least four times the odds of having no disability recorded using the CHAQ (cJADAS10 only: OR 4.5 (95% CI 2.2 to 9.5), both CID: OR 5.2 (95% CI 2.7 to 9.9)) than those with active disease. When assessing non-zero CHAQ scores, CYP who had achieved CID on the cJADAS10 had 50% lower scores (cJADAS10 only: 95% CI 20% to 60%, both CID 95% CI 30% to 70%). Too few CYP in any CID state scored CHQ psychosocial<30, so associations with this outcome could not be tested.

### 6.3.6.4 Association between Early MDA vs. CID on cJADAS10 and Outcomes Measured at One Year

Compared with CYP who met the threshold for MDA on the cJADAS but did not also achieve CID, those that did achieve CID had greater odds of no limited joints (OR 2.4 (95% CI 1.3 to 4.5)) and lower pain VAS scores (coefficient 6.5mm (95% CI 0.9mm to 12.1mm) at one year. However, there were no significant differences in any of the CHAQ or CHQ psychosocial outcomes between these two groups of CYP (Table 27).

**Table 27.** Multivariable associations between disease activity and outcomes at one year following initial presentation to rheumatology

| Disease state at one year following presentation | OR of CHAQ=0 (95% CI) | P-value | IRR of higher CHAQ if CHAQ >0 (95% CI) | P-value | OR for no limited joints (95% CI) | P-value | Coefficient higher CHQ psychosocial (95% CI) | P-value | Coefficient greater pain (mm) (95% CI) | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| **CID states** | | | | | | | | | | |
| Not in CID on either tool | Reference | - | Reference | - | Reference | - | Reference | - | - | - |
| CID Wallace's preliminary criteria only | 0.8 (0.3, 3.2) | 0.975 | 1.1 (0.8, 1.5) | 0.503 | **7.5 (2.9, 19.2)** | **<0.001** | 3.1 (-3.3, 9.5) | 0.335 | - | - |
| CID cJADAS10 only | **4.5 (2.2, 9.5)** | **<0.001** | **0.5 (0.4, 0.8)** | **0.002** | **3.9 (2.5, 6.3)** | **<0.001** | **5.3 (0.5, 10.1)** | **0.029** | - | - |
| CID on both Wallace's preliminary criteria and cJADAS10 | **5.2 (2.7, 9.9)** | **<0.001** | **0.5 (0.3, 0.7)** | **<0.001** | **9.3 (4.9, 17.7)** | **<0.001** | **5.5 (1.5, 9.4)** | **0.007** | - | - |
| **CID vs. MDA on the cJADAS10** | | | | | | | | | | |
| MDA only | Reference | | Reference | | Reference | | Reference | | Reference | |
| CID | 2.6 (1.0, 7.2) | 0.063 | 0.8 (0.5, 1.2) | 0.265 | **2.4 (1.3, 4.5)** | **0.006** | -0.3 (-5.3, 4.8) | 0.914 | **-6.5 (-12.1, -0.9)** | **0.023** |

Bold=p<0.05. Multivariable models adjusted for age (yrs) and disease duration (months) at presentation, gender, hospital and ILAR category (persistent oligo, extended oligo, RF- poly, RF+ poly). CID/MDA states were imputed under various outcomes (see methods) and outcomes were imputed under 'missing at random' assumptions except for CHQ scores, which were analysed under complete case analyses (n=343). OR: Odds ratio, CHAQ: Childhood Health Assessment Questionnaire, IRR: Incidence Rate Ratio, CHQ: Child Health Questionnaire, CID: Clinically inactive disease, MDA: Minimal disease activity, cJADAS10: Clinical Juvenile Arthritis Disease Activity Score using 10 joints

### 6.3.6.5 Associations between Disease Activity State at One Year and Long-term Outcomes

Early achievement of any state of CID was associated with between 2.0 (cJADAS only, 95% CI 1.5 to 2.9) and 3.0 (Wallace only: 95% CI 1.4 to 4.5, both CID: 95% CI 2.0 to 4.5) times the odds of no limited joints for each additional year to five years compared with CYP who had active disease at one year. Achievement of CID on the cJADAS10 was associated with better scores on the CHQ psychosocial score (cJADAS only: β=4.1, 95% CI 1.8 to 6.4, both CID: β=3.9, 95% CI 1.6 to 6.2) and higher probability of both no disability and lower disability among those with non-zero CHAQ scores compared to those with active disease. There was no difference in long-term CHAQ or CHQ scores between CYP who had active disease at one year and those in CID according to Wallace's preliminary criteria but not the cJADAS10.  There was no difference in the proportion of CYP with CHQ scores <30 across all groups.  (Table 28, Figure 18).
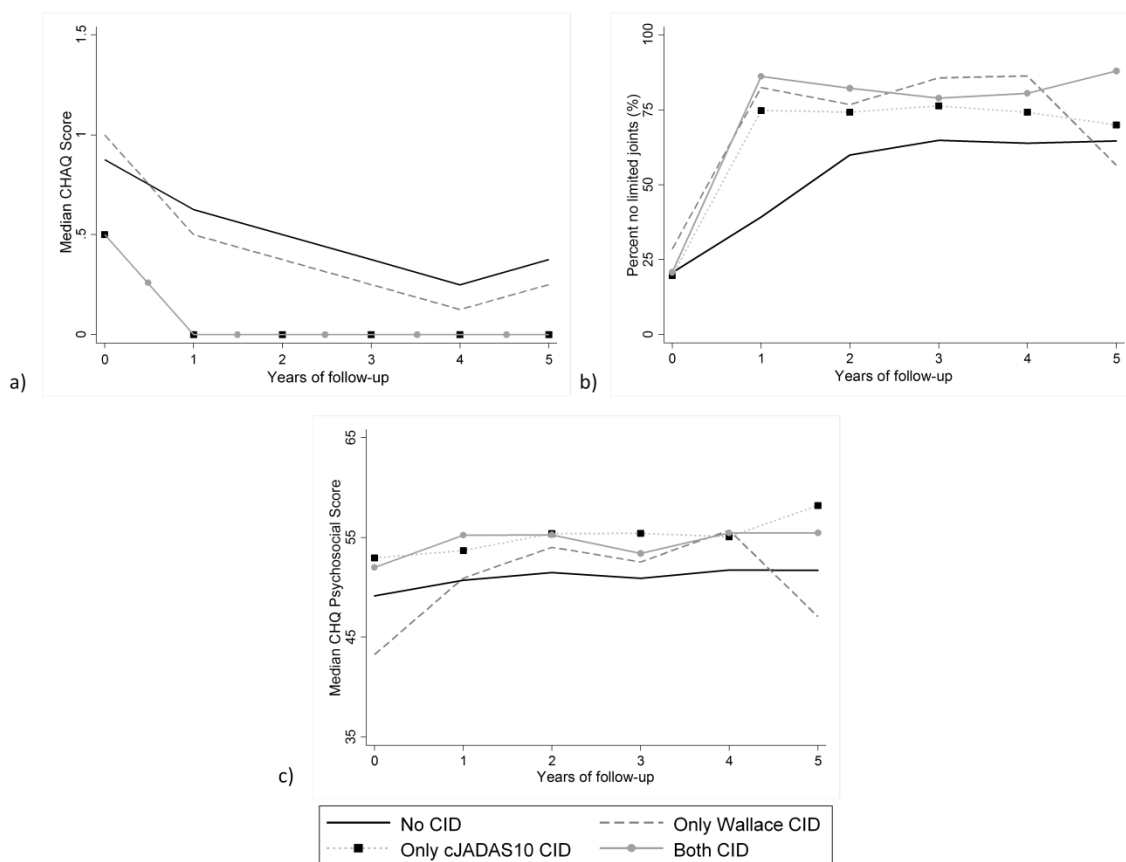


**Figure 18.** Median/percent in outcomes over the five years following initial presentation to paediatric rheumatology, split according to CID state at one year: a) CHAQ scores, b) No limited joints, c) CHQ psychosocial scores. In a), CID on both and cJADAS10 only follow the same median CHAQ scores over five years.

Compared with CYP who had achieved MDA but not CID on the cJADAS10, those who had achieved CID at one year had, on average with each increasing year, 1.7 times the odds of no limited joints (95% CI 1.0 to 2.7) and 5.5mm better pain scores (95% CI 0.9mm to 10.1mm) to five years. There was no difference in CHAQ or CHQ scores between these patient groups (Table 28, Figure 19).
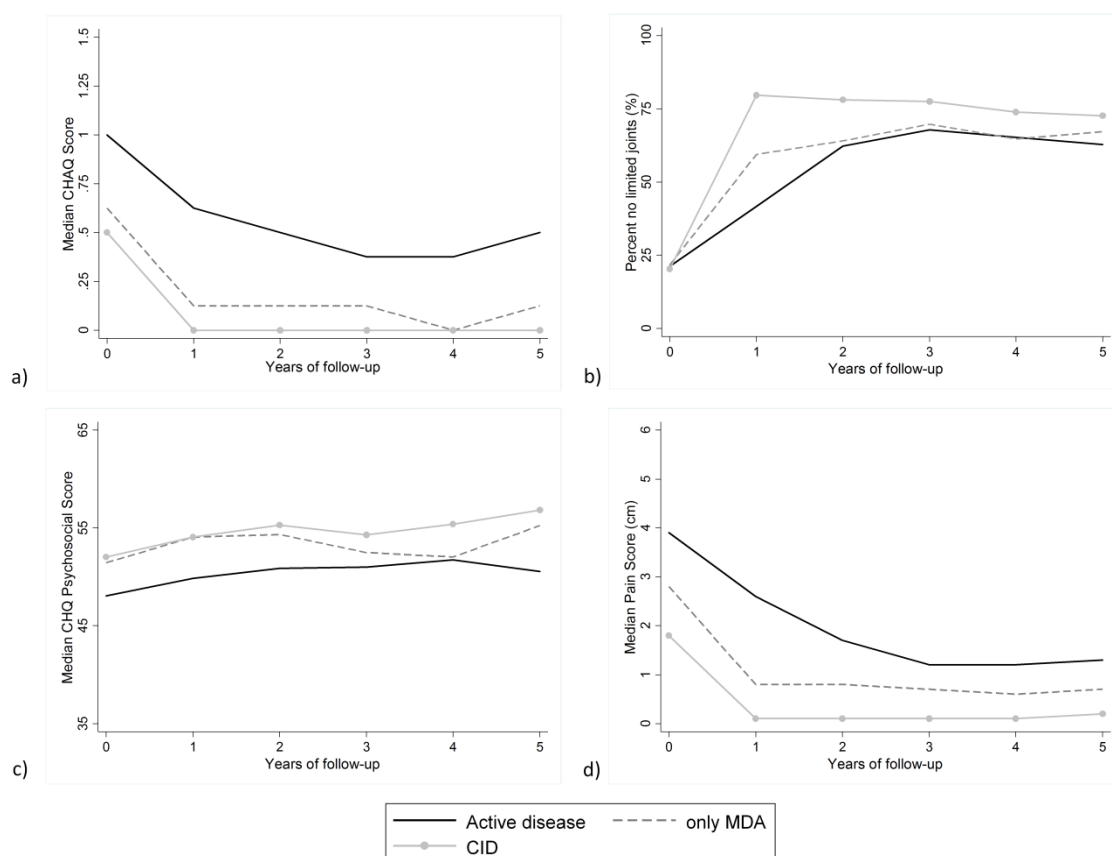


**Figure 19.** Median/percent in outcomes over the first five years following initial presentation to paediatric rheumatology split according disease state on the cJADAS10: a) CHAQ scores, b) No limited joints, c) CHQ scores, d) Pain.

**Table 28.** Multivariable associations between one year disease states and outcomes over the first five years following initial presentation

| Outcome definition at 1 year following presentation | OR of CHAQ=0 (95% CI) | P-value | IRR of higher CHAQ if CHAQ>0 (95% CI) | P-value | OR for no limited joints (95% CI) | P-value | Coefficient higher CHQ psychosocial (95% CI) | P-value | OR CHQ psychosocial <30 (95% CI) | P-value | Coefficient greater pain (mm) (95% CI) | P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CID states** | | | | | | | | | | | | |
| Not in CID on either tool | Reference | - | Reference | - | Reference | - | Reference | - | Reference | - | - | - |
| CID Wallace's preliminary criteria only | 0.8 (0.4, 1.4) | 0.364 | 1.1 (0.9, 1.3) | 0.389 | **2.5 (1.4, 4.5)** | **0.002** | -0.1 (-3.8, 3.5) | 0.944 | 1.8 (0.4, 8.6) | 0.469 | - | - |
| CID cJADAS10 only | **2.5 (1.8, 3.6)** | **<0.001** | **0.7 (0.6, 0.9)** | **0.001** | **2.0 (1.5, 2.9)** | **<0.001** | **4.1 (1.8, 6.4)** | **0.001** | 0.3 (0.1, 1.2) | 0.086 | - | - |
| CID on both Wallace's preliminary criteria and cJADAS10 | **2.5 (1.8, 3.5)** | **<0.001** | **0.8 (0.7, 0.9)** | **0.002** | **3.0 (2.0, 4.5)** | **<0.001** | **3.9 (1.6, 6.2)** | **0.001** | 0.3 (0.1, 1.2) | 0.085 | - | - |
| **CID vs. MDA on the cJADAS10** | | | | | | | | | | | | |
| MDA only | Reference | - | Reference | - | Reference | - | Reference | - | Reference | - | Reference | - |
| CID | 1.5 (0.9, 2.6) | 0.113 | 0.9 (0.8, 1.2) | 0.540 | **1.7 (1.0, 2.7)** | **0.045** | 0.6 (-2.6, 3.9) | 0.712 | 1.3 (0.1, 12.6) | 0.844 | **-5.5 (-10.1, -0.9)** | **0.020** |

Bold=p<0.05. Multivariable models adjust for age (yrs) and disease duration (months) at presentation, gender and ILAR category (persistent oligo, extended oligo, RF-poly, RF+ poly). Missing CID/MDA data were imputed under various assumptions (see methods) and outcome data were imputed under the assumption of data 'missing at random', except for CHQ scores, which were analysed using complete case analysis (n=601)., OR: Odds ratio, CHAQ: Childhood Health Assessment Questionnaire, IRR: Incidence rate ratio, CHQ: Child Health Questionnaire, CI: confidence interval, CID: Clinically inactive disease, MDA: Minimal disease activity, cJADAS10: Clinical Juvenile Arthritis Disease Activity Score in 10 joints

### 6.3.7 Discussion

The success of treat-to-target strategies in adult rheumatology, such as aiming for a low 28-joint count disease activity score (DAS28) [383,384], has prompted the consideration of similar strategies in paediatric practice [152,157,385-387]. One central barrier to implementing treat-to-target approaches in JIA is the lack of a single 'best' target. Although most would agree that CID is the ultimate target, there are multiple ways in which this disease state can be assessed in the clinical setting. Also important in selecting a "best" outcome measure for clinical practice is understanding how it relates to longer term outcomes. Two such definitions were assessed in this analysis: CID according to Wallace or cJADAS10. These two scores differ by their components. The former is limited to assessments by a physician or laboratory measures of inflammation. It also includes an assessment of uveitis activity [237]. CID on the cJADAS10 captures both a lack of inflammation, as assessed by the physician albeit with fewer components but also includes an assessment by the patient/parent [186]. It does not include uveitis activity. The results of this analysis show that CYP who achieve CID at 1 year according to either measure have lower limited joint counts both at 1 year and over the next 4 years of follow-up. However, CYP who achieved CID according to Wallace's preliminary criteria but not cJADAS10 were consistently found to have high levels of disability and poorer psychosocial function. Previous analysis has shown that this difference is driven by lower levels of patient wellbeing, despite the absence of active joints or other inflammatory manifestations of disease [398].

This study benefitted from a large sample of patients with JIA in all three ILAR categories assessed, all treated within a single health care service. The scale of the data collected meant that five year outcomes could be assessed following early achievement of different CID states. In addition, robust methods, including imputation methods under clinically plausible assumptions, were implemented to deal with the inevitable missing data associated with observational cohorts. In particular, a large proportion of patients were lost-to-follow-up. Informative drop-out in the majority of cases informed the imputation methods for CID/MDA states. In turn, this information was used to impute missing outcome values. Thus, although precision of model estimates are affected by missing data, the point estimates should be relatively unbiased.

A challenge is in understanding how best to apply these results in the clinical setting. As achievement of CID according to cJADAS10 was associated with equivalent or superior outcomes to Wallace's preliminary criteria and it is more feasible to complete in clinical practice, due to containing only three routinely collected components [198], one could argue

that this is likely to be a superior treatment target for application in clinical practice. However, a number of limitations of both the outcome measure and the analysis should be considered.

As the two scores differ in their components one could argue that they are not capturing the same construct. Wallace's preliminary criteria capture more objective measures of inflammation whilst the cJADAS10, through inclusion of a patient wellbeing measure, may also capture other non-inflammatory components of the disease, such as chronic pain and fatigue not captured by Wallace's preliminary criteria. However, in addition to a single score/cut-off, the value of the individual components of the cJADAS10 would be required to guide individual treatment decisions. Although it is well recognised that functional ability, HRQoL and pain do improve following treatment with both methotrexate and biologic therapies [402-407], treating to a cJADAS target may also require a multifactorial treatment strategy, potentially including interventions such as physiotherapy and psychological services for CYP with chronic pain in the absence of active joints. Otherwise there is the risk of intensifying or changing immunosuppressive therapy in the absence of inflammation. Equally, relying solely on Wallace's preliminary criteria may guide immunosuppressive therapy very well, but may ignore other symptoms relevant to the patient.

At the outset of this analysis, it was also unknown whether achievement of CID is associated with better outcomes compared to those who achieve MDA but not CID. This study found that that achieving CID on the cJADAS10 is associated with a greater absence of limited joints compared with MDA. However, achieving CID above MDA was not associated with greater improvements in CHAQ or CHQ scores either between baseline and one year, or from one to five years. Therefore, MDA on the cJADAS10 may be an appropriate target when disease activity parameters are low but patient wellbeing is poor. The risk of adverse effects with treatment intensification should be considered, particularly if the attainment of CID is deemed unlikely [408] or patient wellbeing is high.

A limitation of this study was that, to avoid circular reasoning, important disease activity variables such as active joint counts could not be used as outcomes. Since the variables differentially form the CID states, any state including said variable would be intrinsically more likely to associate with the outcome. The outcomes selected for the study did, however, comprise multiple physician and patient-important outcomes. However, these conclusions can only relate to oligoarticular and polyarticular JIA. The CID definitions have only been validated in these categories and it is likely that additional components will

need to be added to these criteria sets in order to fully capture low and inactive disease in less common JIA categories. In addition, due to a lack of data on morning stiffness, we were not able to compare outcomes following the achievement of the 2011 ACR CID criteria with the other CID states. Finally, although it has been suggested that treat-to-target strategies will result in better long term outcomes, during the period of data collection for this study, there was no formal treat-to-target strategy in place in the UK. Therefore although the findings support that early achievement of CID is associated with better outcomes, the data cannot be used to show that active treatment towards these targets currently results in better long term outcomes. Further work will need to assess long-term outcomes following the implementation of these guidelines.

### 6.3.8   Conclusion

Early achievement of cJADAS10 CID is associated with equivalent or superior long-term outcomes compared with CID on Wallace's preliminary criteria. Differences in the components of these two definitions and the implications for clinical practice through implementation of a single score suggest that the optimal definition for CID for application in a clinical setting remains unclear. Further work, ideally involving consumers, clinicians and researchers, is needed to best define treatment targets and treatment strategies, for use in JIA. The results do, however, highlight the importance of addressing all aspects of JIA and not just the underlying inflammation, in terms of best outcomes for the child.

### 6.3.9   Acknowledgements

### 6.3.10 Supplementary Materials

**Supplementary Table 9.** Proportion of available of data across outcomes and time points in the study cohort

| Outcome | Total number in analysis (max n=832) | Data available at each time point (N, %)[1] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
| CHAQ | 768 | 554 (72) | 573 (75) | 514 (67) | 465 (61) | 414 (54) | 351 (46) |
| Limited joint count | 827 | 785 (95) | 677 (82) | 568 (69) | 459 (56) | 330 (40) | 224 (27) |
| CHQ psychosocial | 643[2] | 281 (44) | 343 (53) | 342 (53) | 356 (55) | 347(54) | 290 (45) |
| Pain | 770 | 553 (72) | 572 (74) | 512 (66) | 461 (60) | 414 (54) | 353 (46) |

[1]Percent out of CYP included in the analysis for the corresponding outcome [2] 601 CYP available for longitudinal analysis, 343 used in the analysis at one year. CHAQ: Childhood Health Assessment Questionnaire, CHQ: Child Health Questionnaire

**Supplementary Table 10.** Multivariable associations between disease activity and outcomes at one year following initial presentation to rheumatology under complete case analyses

| Disease state at one year following presentation | OR of CHAQ=0 (95% CI) | P-value | IRR of higher CHAQ if CHAQ >0 (95% CI) | P-value | OR for no limited joints (95% CI) | P-value | Coefficient higher CHQ psychosocial (95% CI) | P-value | Coefficient greater pain (mm) (95% CI) | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| **CID definitions** | | | | | | | | | | |
| Not in CID on either tool | Reference | - | Reference | - | Reference | - | Reference | - | - | - |
| CID Wallace's preliminary criteria only | 0.7 (0.1, 5.1) | 0.710 | 1.1 (0.7, 1.5) | 0.751 | **7.1 (2.7, 18.6)** | **<0.001** | 3.1 (-3.3, 9.5) | 0.335 | - | - |
| CID cJADAS10 only | **4.8 (1.3, 16.9)** | **<0.015** | **0.5 (0.3, 0.9)** | **0.025** | **4.2 (2.6, 6.8)** | **<0.001** | **5.3 (0.5, 10.1)** | **0.029** | - | - |
| CID on both Wallace's preliminary criteria and cJADAS10 | **5.5 (2.1, 14.4)** | **0.001** | **0.5 (0.3, 0.7)** | **<0.001** | **8.6 (4.8, 15.5)** | **<0.001** | **5.5 (1.5, 9.4)** | **0.007** | - | - |
| **CID vs. MDA on the cJADAS10** | | | | | | | | | | |
| MDA only | Reference | | Reference | | Reference | | Reference | | Reference | |
| CID | 3.4 (0.8, 14.2) | 0.088 | 0.7 (0.4, 1.1) | 0.088 | **2.3 (1.2, 4.4)** | **0.015** | -0.3 (-5.3, 4.8) | 0.914 | -6.7 (-15.0, 1.6) | 0.113 |

Bold=p<0.05. Multivariable models adjust for age (yrs), disease duration (months) and calendar year at presentation, gender and ILAR subtype (persistent oligo, extended oligo, RF- poly, RF+ poly). Missing CID/MDA states were imputed using a combination of assumptions (see methods) and all outcomes were analysed using complete case analyses. CID: Clinically inactive disease; MDA: Minimal disease activity; cJADAS10: Clinical Juvenile Arthritis Disease Activity Score using a 10 joint count; CHAQ: Childhood Health Assessment Questionnaire; CHQ: Child Health Questionnaire; CI: Confidence interval; IRR: Incidence risk ratio; OR: Odds ratio

**Supplementary Table 11.** Multivariable associations between one year disease states and outcomes over the first five years using complete case analyses

| Outcome definition at 1 year following presentation | IRR of CHAQ=0 (95% CI) | P-value | IRR of higher CHAQ if CHAQ>0 (95% CI) | P-value | OR for no limited joints (95% CI) | P-value | Coefficient higher CHQ psychosocial (95% CI) | P-value | OR CHQ psychosocial <30 (95% CI) | P-value | Coefficient greater pain (mm) (95% CI) | P-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CID states** | | | | | | | | | | | | |
| Not in CID on either tool | Reference | - | Reference | - | Reference | - | Reference | - | Reference | - | - | - |
| CID Wallace's preliminary criteria only | 0.7 (0.4, 1.4) | 0.301 | 1.1 (0.9, 1.5) | 0.350 | **3.7 (1.9, 7.2)** | **<0.001** | -0.1 (-3.8, 3.5) | 0.944 | 1.8 (0.4, 8.6) | 0.469 | - | - |
| CID cJADAS10 only | **3.0 (1.9, 4.6)** | **<0.001** | **0.6 (0.4, 0.8)** | **0.002** | **2.4 (1.7, 3.5)** | **<0.001** | **4.1 (1.8, 6.4)** | **0.001** | 0.3 (0.1, 1.2) | 0.086 | - | - |
| CID on both Wallace's preliminary criteria and cJADAS10 | **3.0 (2.0, 4.5)** | **<0.001** | **0.7 (0.5, 0.9)** | **0.003** | **4.5 (2.8, 7.1)** | **<0.001** | **3.9 (1.6, 6.2)** | **0.001** | 0.3 (0.1, 1.2) | 0.085 | - | - |
| **CID vs. MDA on the cJADAS10** | | | | | | | | | | | | |
| MDA only | Reference | - | Reference | - | Reference | - | Reference | - | Reference | - | Reference | - |
| CID | 1.6 (0.9, 3.1) | 0.130 | 0.8 (0.6, 1.1) | 0.188 | **2.2 (1.3, 3.7)** | **0.003** | 0.6 (-2.6, 3.9) | 0.712 | 1.3 (0.1, 12.6) | 0.844 | **-6.4 (-11.4, -1.4)** | **0.012** |

Bold=p<0.05. Multivariable models adjust for age (yrs), disease duration (months) and calendar year at presentation, gender and ILAR subtype (persistent oligo, extended oligo, RF- poly, RF+ poly). Missing CID/MDA states were imputed using a combination of assumptions (see methods) and all outcomes were analysed using complete case analyses. CID: Clinically inactive disease; MDA: Minimal disease activity; cJADAS10: Clinical Juvenile Arthritis Disease Activity Score using a 10 joint count; CHAQ: Childhood Health Assessment Questionnaire; CHQ: Child Health Questionnaire; CI: Confidence interval; IRR: Incidence risk ratio; OR: Odds ratio
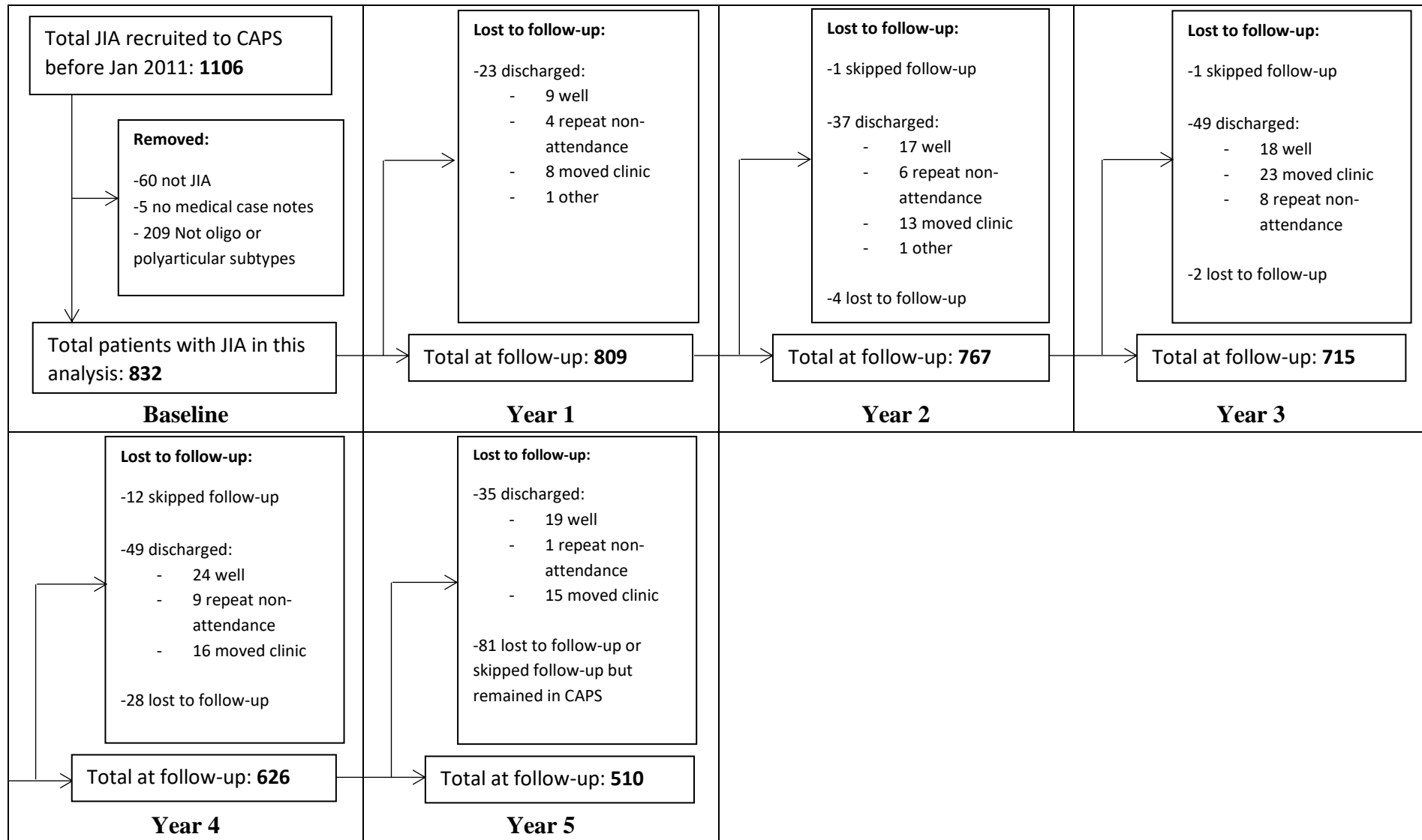
**Supplementary Figure 1**. Patient flow through the study

## 6.4 Factors Associated with Remission in a Prospective Cohort of Patients with Juvenile Idiopathic Arthritis: the Importance of Definition

**Currently prepared for planned submission to Annals of the Rheumatic Diseases**

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**Word count (excluding references):** 3340

**Key words:** Juvenile idiopathic arthritis, Remission, Inactive disease, Treatment target

### 6.4.2 Abstract

**Background:** Certain characteristics may predispose a patient with JIA to the achievement or non-achievement of remission. It is not currently known if factors associated with remission in JIA differ based on how remission is defined.

**Methods:** Children and young people (CYP) enrolled in the Childhood Arthritis Prospective Study, a UK multicentre inception cohort, were selected if diagnosed with persistent or extended oligoarthritis, RF-negative or RF-positive polyarticular JIA before January 2014.

Remission was defined as two consecutive annual time points in CID according to i) Wallace's preliminary criteria or ii) CID on clinical Juvenile Arthritis Disease Activity Score using 10 joints (JADAS10). Demographic features, JIA core outcome variables at initial presentation and changes in disease-related variables over the first year were tested for associations with remission using multivariable logistic regression models. Multiple imputation accounted for missing factor and outcome data.

**Results:** Of 1045 CYP, the majority were female (70%) and had oligoarthritis (67%). Within three years, 25% had achieved remission using Wallace's preliminary criteria and 39% using the cJADAS10.

Older age at initial presentation was associated with remission using Wallace's preliminary criteria whilst multiple patient-reported factors and living in a lesser deprived area were associated with remission using the cJADAS10. Greater improvements in both signs and symptoms of JIA over the first year were associated with remission, although improvement in a greater number of factors was associated with remission using the cJADAS10.

**Conclusions:** Greater improvements in disease over the first year following diagnosis were associated with future remission. Different factors were associated with remission depending on how it was defined.

### 6.4.3 Introduction

In current practice, only approximately half of patients with JIA achieve remission after as many as ten to twenty years of disease [409]. The reasons some patients do not achieve remission are not known, but may relate to sociodemographic factors, features of their disease or the effectiveness of different treatments or treatment strategies. Those with lower chances of achieving remission may benefit from earlier, more aggressive or alternative therapeutic strategies. This treatment stratification would maximise patient benefit and minimise the risk of adverse effects from unnecessary treatments.

A challenge within paediatric rheumatology is the lack of a single definition of remission [152,409]. Previous studies have identified that different validated definitions for clinically inactive disease (CID) and remission identify different groups of children and young people (CYP) [410]. It has also been shown that longer term outcomes, among CYP who achieve CID at one year according to different definitions, vary [411]. Thus, when aiming for stratified approaches to treatment in JIA, it is unclear whether different factors may associate with remission depending on how it is defined.

Predicting remission in JIA would be ideal at the point of presentation, where a child or young person (CYP) with JIA has experienced relatively little therapy and may stand to benefit the most from a stratified treatment approach [291,412]. In addition, changes in disease characteristics in the short-term following this time-point may add additional information regarding associations between response to therapies and future remission. However, very few patient or disease characteristics at initial presentation have consistently been associated with later remission [413]. Age at diagnosis [272,273], physician [273,281] and parental global assessments [273,281] and CHAQ scores [6,257,273,281] have been associated with remission inconsistently across studies. One consistent predictor of remission in JIA across cohorts, however, is ILAR category. Patients with oligoarticular disease consistently have better outcomes than those with other ILAR categories [413]. Given the differences in the features of disease [1] and treatment strategies [24,414] for the different ILAR categories, it is plausible that different predictors of remission may exist within these disease subtypes.

Factors associated with remission have rarely been explored further than univariable models, not at first presentation to rheumatology or using published definitions of remission, such as those according to Wallace's preliminary criteria [237] or JADAS scores [186]. None have explored whether the definition of remission matters.

The aims of the current analysis were therefore to identify independent factors associated with remission in JIA, incorporating patient and disease characteristics at, and changes

over the first year following, initial presentation to paediatric rheumatology. To explore the impact of the definitions of remission, analyses were carried out separately for remission according to (a) Wallace Preliminary Criteria [237] and (b) clinical Juvenile Arthritis Disease Activity Score using a 10 joint count (cJADAS10) [186]. These analyses were limited to CYP with oligoarthritis (persistent and extended) and polyarthritis (RF-negative and positive) JIA only.

### 6.4.4 Methods

#### 6.4.4.1 Study Population

The study population was selected from the Childhood Arthritis Prospective Study (CAPS), a UK, multicentre inception cohort of childhood-onset inflammatory arthritis. The study began recruitment in 2001 and is the largest inception cohort of JIA globally, with over 1600 participants recruited to date [297]. Ethical approval for CAPS was gained from the Northwest Multicentre Ethics Committee and written informed consent was gained from families of participants, with assent from participants where appropriate.

Patients from CAPS were selected for the current study if they had persistent or extended oligoarthritis, RF-negative or RF-positive polyarticular categories of JIA and had been recruited to CAPS prior to January 2014, to allow for at least three years of follow-up. Participants with no returned study forms after initial recruitment were excluded.

#### 6.4.4.2 Data Collection

The CAPS baseline date was initial presentation to paediatric rheumatology and data were collected from the medical record at this time point and at one year following this date using a pre-defined study proforma. Demographic data, features of disease activity, ILAR category and anti-rheumatic medications were captured. At baseline and then annually, patients and their guardians were asked to complete a series of questionnaires including the Childhood Health Assessment Questionnaire (CHAQ) [188], a measure of functional ability (scores range from 0 to 3), 100mm pain and 100mm wellbeing (PGE) visual analogue scores (VAS) (all completed by patient if ≥11 years, otherwise proxy-completion). Collection of CID criteria has been previously described [410].

#### 6.4.4.3 Outcome Definitions

At each annual follow-up to three years, CYP were classified as to whether they had fulfilled i) CID on Wallace's preliminary criteria [165] and ii) CID on the cJADAS10 [186]. CID on Wallace's preliminary criteria was defined as no active joints, 0cm on the PGA,

normal ESR/CRP, no uveitis and no systemic features in systemic JIA [165]. CID on the cJADAS10 was defined as a summed score ≤1 using active joints in a maximum of ten joints, PGA and PGE scores [186]. Modified remission criteria for each definition were defined as two consecutive time points in CID at any point from one to three years of follow-up. Medication was not considered as part of either definition.

### 6.4.4.4 Selection of Potential Factors Associated with Remission

Variables assessed at baseline and one year for associations with remission included demographic features: age at initial presentation, gender, ethnicity, and socioeconomic status using the English index of multiple deprivation (IMD) [72]. The English IMD is a national measure based on multiple indices of economic deprivation, such as employment and income, and social deprivation, such as access to housing and crime, relative across locations of residence. Scores were only assigned to CYP residing in England (81%), as similar scores in the remainder of the UK are not directly comparable. IMD scores were split into population quintiles based on the English 2015 indices [72] and analysed between the 20% most deprived, 60% central scores and 20% least deprived areas. Clinical features included disease duration at initial presentation, active and limited joint counts, PGA, ESR, PGE, CHAQ and pain.

### 6.4.4.5 Statistical Analyses

#### The Achievement of CID and Remission

The frequency and proportion of CYP that achieved CID at one year and remission within three years were explored descriptively for the entire cohort and within oligoarthritis and polyarthritis groups separately. ILAR category was assigned using data collected at one year to allow 'settling' into a category. If that was not recorded, the nearest ILAR category recoded closest in time was used, with an earlier recorded ILAR category preferred.

#### Predictors at initial presentation of remission within three years

Initially, univariable logistic regression analyses assessed associations between baseline variables and the remission states. Multivariable models included patient characteristics (gender, age at initial presentation and ethnicity (white versus non-white)) in addition to the JIA core outcome variables and symptom duration at initial presentation. Due to collinearity between the patient/parent global assessment and pain (Spearman's r=0.8), pain was excluded from consideration, as it does not form part of the JIA core outcome variables [161]. Models were developed for each remission definition for patients with

oligoarthritis and polyarthritis separately. An additional restricted analysis was performed to test IMD as a predictor in CYP among CYP resident in England only.

*Associations between Factors at One year and Remission within Three Years*

Changes in physician or patient-reported measures over the first year were calculated. Univariable logistic regression analyses assessed associations between these factors and the achievement of remission according to the two definitions. In addition, multivariable models assessed these associations adjusting for gender, age at initial presentation, ethnicity, the respective variable at baseline, glucocorticoid (yes/no) therapy within the first year in oligoarthritis and conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy within the first year in polyarthritis.

Missing variable data were imputed using multiple imputation using chained equations over 20 iterations under the assumption of data missing at random (MAR). Missing outcome data were imputed under assumptions previously defined (Supplementary Materials) [398], with CYP that skipped follow-up appointments assumed to have CID at the time point skipped according to both definitions. An additional imputation model was constructed for predictor and outcome data for CYP with complete English IMD scores. Sensitivity analyses assumed all missing data were MAR. Analyses were undertaken in STATA 14 (Stata Corp, College Station, TX, USA).

### 6.4.5   Results

#### 6.4.5.1 Patient Cohort

To 1st January 2014, a total of 1510 CYP had been recruited to CAPS. Of these, 60 did not have JIA and 369 had been diagnosed with an ILAR category not included in this analysis. Thirty two CYP had no returned study forms, three were prevalent cases at enrollment and one CYP died prior to year three (and was thus excluded), leaving 1045 participants in the analysis. Seventy percent were female, the median age at initial presentation to paediatric rheumatology was seven years (IQR 3 to 11), the majority had oligoarthritis (67%; 93% of these had persistent oligoarthritis). As expected, CYP with polyarthritis had higher levels of disease activity and higher use of csDMARDs (72% in polyarthritis, 21% in oligoarthritis) and biologic therapies (22% in polyarthritis, 2% in oligoarthritis) compared with those with oligoarthritis within the first year following initial presentation (Table 29).

### *6.4.5.2 Achievement of CID and Remission*

At three years, 851 CYP remained in the study (Supplementary Figure 2). At one year following initial presentation, 34% of patients with oligoarthritis and 27% of those with polyarthritis had achieved CID according to Wallace's preliminary criteria. In contrast, 50% and 34% had achieved CID according to the cJADAS10, respectively. Fewer had achieved remission with 27% of patients with oligoarthritis and 20% of those with polyarthritis having achieved remission according to Wallace's preliminary criteria and 45% of CYP with oligoarthritis and 28% of those with polyarthritis ever having achieved remission according to the cJADAS10 (Figure 20).

**Table 29.** Baseline characteristics of the cohort

| Baseline characteristic | % data available | Oligoarthritis (n=704) | Polyarthritis (n=341) |
|---|---|---|---|
| | | **Median (IQR) or N (%)** | |
| **Demographic factors** | | | |
| Female | 100 | 469 (66) | 266 (78) |
| White or Caucasian | 98 | 622 (90) | 304 (91) |
| **Index of multiple deprivation** | >99% for England (n=821/824) | | |
| In 20% most deprived areas | | 166 (29) | 76 (30) |
| In 60% middle IMD areas | | 303 (53) | 129 (52) |
| In 20% least deprived areas | | 105 (18) | 45 (18) |
| Age at onset (years) | 99 | 5.3 (2.3, 9.7) | 6.7 (2.7, 10.6) |
| Age at initial presentation (years) | 100 | 6.5 (3.0, 11.0) | 8.2 (3.6, 11.6) |
| Symptom duration at initial presentation (months) | 99 | 5.5 (2.9, 11.5) | 5.7 (3.3, 12.0) |
| **Disease activity** | | | |
| Active joint count | 91 | 1 (1, 2) | 7 (4, 14) |
| Limited joint count | 91 | 1 (1, 2) | 5 (2, 10) |
| Physician's global assessment (cm) | 69 | 2.2 (1.2, 3.8) | 4.4 (2.8, 6.4) |
| ESR (mm/hr) | 62 | 14 (5, 28) | 30 (10, 60) |
| CRP (mg/L) | 58 | 5 (4, 9) | 14 (5, 44) |
| ILAR category at one year | 100 | Persistent: 635 (90%) | RF negative: 293 (86%) |
| | | Extended: 69 (10%) | RF positive: 48 (14%) |
| **Patient-reported factors** | | | |
| Parent/patient global evaluation (cm) | 67 | 1.7 (0.3, 4.9) | 3.5 (1.1, 5.7) |
| Pain (cm) | 68 | 2.3 (0.7, 5.0) | 4.6 (1.3, 7.0) |
| Function: CHAQ | 69 | 0.6 (0.1, 1.1) | 1.3 (0.6, 1.8) |
| **Treatments in the first year** | | | |
| Steroid* | 100 | 481 (68) | 237 (70) |
| csDMARD | 100 | 151 (21) | 245 (72) |
| Biologic | 100 | 15 (2) | 75 (22) |

*Steroids administered any route. IQR: Interquartile range, IMD: Index of multiple deprivation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CHAQ: Childhood Health Assessment Questionnaire, CHQ: Child Health Questionnaire, GHQ: General Health Questionnaire, csDMARD: Conventional synthetic disease-modifying anti-rheumatic drug.
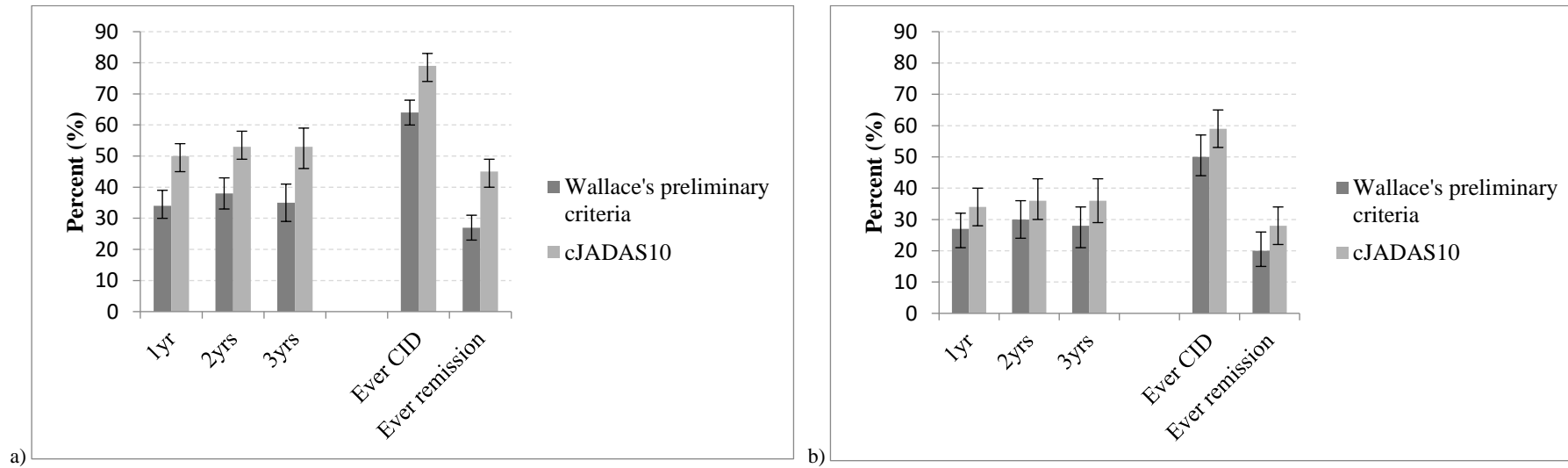
**Figure 20.** Achievement of CID at annual follow-ups to three years and cumulative achievement of CID and remission over the first three years following initial presentation to paediatric rheumatology in a) oligoarthritis b) polyarthritis.

### 6.4.5.3 Factors at Initial Presentation Associated with Remission within Three Years

For remission defined according to Wallace's preliminary criteria, increased age at initial presentation to paediatric rheumatology was associated with 7% higher odds of remission in oligoarthritis (95% CI 1% to 12%) and 10% higher odds in polyarthritis (95% CI 2% to 18%) in univariable analyses. These associations remained after adjusting for other factors in the multivariable model (Table 30).

For remission defined according to the cJADAS10, age at initial presentation was not an associated factor. Instead, increased CHAQ and PGE scores at initial presentation were associated with 35% (95% CI 9% to 53%) and 11% (95% CI 3% to 19%) lower odds of remission in univariable analyses in CYP with oligoarthritis, respectively. In polyarthritis, increased CHAQ but not PGE scores at this time were associated with 35% (95% CI 5% to 56%) lower odds of remission in univariable analyses. However, these factors were not significantly associated with remission in multivariable analyses (Table 30).

In the analysis restricted to CYP residing in England, living in the least deprived areas was associated with higher odds of remission. Compared with those living in the 20% most deprived areas, those living in the central 60% and 20% least deprived areas had 1.8 (95% CI 1.0, 3.1) and 2.3 (95% CI 1.1, 4.6) times the odds of remission, respectively. Whilst point estimates were similar across CYP with oligoarthritis and polyarthritis, this association was only statistically significant in those with oligoarthritis.

### 6.4.5.4 Associations between Changes over the First Year and Remission within the First Three Years

Improvements in many physician and patient-reported factors over the first year following initial presentation were associated with remission within three years (Table 31). In oligoarthritis, greater improvements in active joint count, ESR, PGA and PGE scores were associated with remission on Wallace's preliminary criteria. These associations remained independent in multivariable analysis. In polyarthritis, greater improvements in the number of limited joints, PGA and PGE scores and, when adjusted for csDMARD therapy (yes/no), CHAQ scores over the first year were associated with remission using Wallace's preliminary criteria. For remission using the cJADAS10, in both oligoarthritis and polyarthritis, greater improvements in active and limited joint counts, CHAQ, PGA and PGE scores were associated with remission (Table 31).

**Table 30.** Factors associated with remission within three years using Wallace's preliminary criteria and the cJADAS10

| Factor at initial presentation to paediatric rheumatology | Wallace's preliminary criteria | | | | cJADAS10 | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | |
| | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| **Oligoarthritis** | | | | | | | | |
| Female | 1.2 (0.7, 2.3) | 0.535 | 1.1 (0.7, 2.0) | 0.621 | 1.1 (0.7, 1.6) | 0.668 | 1.1 (0.8, 1.7) | 0.510 |
| White or Caucasian | 2.5 (0.8, 7.9) | 0.125 | 1.2 (0.6, 2.4) | 0.689 | 1.3 (0.6, 2.6) | 0.485 | 1.2 (0.6, 2.7) | 0.615 |
| Age at initial presentation (years) | **1.1 (1.0, 1.1)** | **0.010** | **1.1 (1.0, 1.1)** | **0.038** | 1.0 (1.0, 10) | 0.946 | 1.0 (1.0, 1.0) | 0.925 |
| Symptom duration at initial presentation (months) | 1.0 (1.0, 1.0) | 0.970 | 1.0 (1.0, 1.0) | 0.391 | 1.0 (1.0, 1.0) | 0.316 | 1.0 (1.0, 1.0) | 0.302 |
| Active joint count | 1.0 (0.9, 1.1) | 0.704 | 1.0 (0.9, 1.1) | 0.925 | 1.0 (0.9, 1.1) | 0.442 | 1.0 (0.9, 1.1) | 0.587 |
| Limited joint count | 1.0 (0.9, 1.1) | 0.752 | 1.0 (0.9, 1.2) | 0.890 | 1.0 (0.9, 1.1) | 0.885 | 1.0 (0.9, 1.2) | 0.505 |
| CHAQ | **0.7 (0.5, 1.0)** | **0.045** | 0.8 (0.9, 1.1) | 0.203 | **0.7 (0.5, 1.0)** | **0.012** | 0.8 (0.5, 1.1) | 0.158 |
| ESR (per 10mm/hr) | 0.9 (0.8, 1.1) | 0.275 | 1.0 (1.0, 1.0) | 0.608 | 1.0 (0.9, 1.1) | 0.401 | 1.0 (1.0, 1.0) | 0.674 |
| PGA (cm) | 0.9 (0.8, 1.1) | 0.358 | 1.0 (0.8, 1.1) | 0.509 | 0.9 (0.9, 1.0) | 0.224 | 1.0 (0.9, 1.1) | 0.557 |
| PGE (cm) | 1.0 (0.9, 1.1) | 0.418 | 1.0 (0.9, 1.1) | 0.979 | **0.9 (0.8, 1.0)** | **0.009** | 0.9 (0.8, 1.0) | 0.161 |
| **Polyarthritis** | | | | | | | | |
| Female | 1.4 (0.7, 2.8) | 0.331 | 1.3 (0.6, 2.8) | 0.498 | 1.6 (0.9, 1.9) | 0.111 | 1.6 (0.9, 3.0) | 0.143 |
| White or Caucasian | 2.2 (0.5, 10.1) | 0.316 | 2.1 (0.4, 11.8) | 0.387 | 2.1 (0.7, 7.0) | 0.209 | 2.1 (0.6, 7.4) | 0.248 |
| Age at initial presentation (years) | **1.1 (1.0, 1.2)** | **0.007** | **1.1 (1.0, 1.2)** | **0.006** | 1.0 (1.0, 1.1) | 0.133 | 1.1 (1.0, 1.1) | 0.107 |
| Symptom duration at initial presentation (months) | 1.0 (1.0, 1.0) | 0.739 | 1.0 (1.0, 1.0) | 0.304 | 1.0 (1.0, 1.0) | 0.645 | 1.0 (1.0, 1.0) | 0.459 |
| Active joint count | 1.0 (1.0, 1.0) | 0.287 | 1.0 (1.0, 1.1) | 0.161 | 1.0 (1.0, 1.0) | 0.997 | 1.0 (1.0, 1.1) | 0.403 |
| Limited joint count | 1.0 (1.0, 1.0) | 0.875 | 1.0 (0.9, 1.0) | 0.271 | 1.0 (1.0, 1.0) | 0.305 | 1.0 (0.9, 1.0) | 0.288 |
| CHAQ | 0.8 (0.5, 1.2) | 0.225 | 0.6 (0.3, 1.2) | 0.133 | **0.7 (0.4, 1.0)** | **0.026** | 0.6 (0.4, 1.0) | 0.070 |
| ESR (per 10mm/hr) | 1.0 (0.9, 1.1) | 0.593 | 1.0 (1.0, 1.0) | 0.651 | 1.0 (0.9, 1.1) | 0.878 | 1.0 (1.0, 1.0) | 0.939 |
| PGA (cm) | 1.0 (0.9, 1.2) | 0.859 | 1.0 (0.8, 1.2) | 0.997 | 1.0 (0.9, 1.1) | 0.939 | 1.0 (0.9, 1.2) | 0.718 |
| PGE (cm) | 1.0 (0.9, 1.2) | 0.630 | 1.1 (0.9, 1.3) | 0.191 | 1.0 (0.9, 1.1) | 0.366 | 1.0 (0.9, 1.2) | 0.752 |

Multivariable models include all variables listed. *Bold=p≤0.05, CID: Clinically inactive disease, cJADAS10: Clinical Juvenile Arthritis Disease Activity Score using 10 joints, CI: Confidence interval, IMD: Index of multiple deprivation, CHAQ: Childhood Health Assessment Questionnaire, ESR: Erythrocyte sedimentation rate, PGA: Physician's global assessment, PGE: Parental global evaluation

**Table 31.** Changes in factors over the first year and remission within three years using Wallace's preliminary criteria and the cJADAS10

| Factor potentially associated with remission | Wallace's preliminary criteria | | | | cJADAS10 | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | |
| | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value | OR (95% CI) | P-value |
| **Oligoarthritis** | | | | | | | | |
| Change in active joint count | 0.9 (0.9, 1.0) | 0.158 | **0.6 (0.4, 1.0)** | **0.040** | 0.9 (0.9, 1.0) | 0.132 | **0.6 (0.5, 0.9)** | **0.010** |
| Change in limited joint count | 0.9 (0.8, 1.1) | 0.364 | 0.8 (0.6, 1.1) | 0.137 | 0.9 (0.8, 1.0) | 0.108 | **0.7 (0.5, 0.9)** | **0.047** |
| Change in CHAQ | 1.1 (0.8, 1.4) | 0.637 | 0.8 (0.5, 1.2) | 0.279 | 0.9 (0.6, 1.1) | 0.281 | **0.4 (0.3, 0.7)** | **<0.001** |
| Change in ESR (per 10mm/hr) | **1.0 (1.0, 1.0)** | **0.032** | **0.9 (0.9, 1.0)** | **0.021** | 1.0 (1.0, 1.0) | 0.233 | 1.0 (1.0, 1.0) | 0.132 |
| Change in PGA (cm) | **0.9 (0.8, 1.0)** | **0.047** | **0.3 (0.2, 0.5)** | **<0.001** | **0.9 (0.8, 1.0)** | **0.006** | **0.5 (0.4, 0.6)** | **<0.001** |
| Change in PGE (cm) | **0.9 (0.8, 1.0)** | **0.025** | **0.7 (0.6, 0.8)** | **<0.001** | **0.9 (0.8, 1.0)** | **0.005** | **0.5 (0.4, 0.7)** | **<0.001** |
| **Polyarthritis** | | | | | | | | |
| Change in active joint count | 1.0 (1.0, 1.0) | 0.073 | 0.7 (0.5, 1.1) | 0.104 | 1.0 (1.0, 1.0) | 0.360 | 0.8 (0.6, 1.0) | 0.052 |
| Change in limited joint count | 1.0 (1.0, 1.0) | 0.444 | **0.8 (0.7, 1.0)** | **0.049** | 1.0 (1.0, 1.0) | 0.925 | **0.9 (0.8, 1.0)** | **0.045** |
| Change in CHAQ | 0.9 (0.6, 1.3) | 0.495 | **0.5 (0.3, 1.0)** | **0.044** | 0.8 (0.6, 1.1) | 0.140 | **0.4 (0.2, 0.7)** | **0.001** |
| Change in ESR (per 10mm/hr) | 1.0 (1.0, 1.0) | 0.266 | 0.9 (0.8, 1.0) | 0.105 | 1.0 (1.0, 1.0) | 0.271 | 1.0 (0.9, 1.0) | 0.090 |
| Change in PGA (cm) | **0.8 (0.7, 1.0)** | **0.013** | **0.2 (0.1, 0.7)** | **0.013** | **0.9 (0.8, 1.0)** | **0.010** | **0.4 (0.3, 0.7)** | **<0.001** |
| Change in PGE (cm) | **0.9 (0.8, 1.0)** | **0.011** | **0.7 (0.5, 0.9)** | **0.003** | **0.9 (0.8, 1.0)** | **0.004** | **0.5 (0.3, 0.8)** | **0.002** |

Multivariable models adjusted for ethnicity (white/not white), gender, age at initial presentation, symptom duration at initial presentation, risk factor at initial presentation and steroids over the first year (yes/no) for oligoarthritis and sDMARDs (yes/no) for polyarthritis. *Bold=p≤0.05, CID: Clinically inactive disease, cJADAS10: Clinical Juvenile Arthritis Disease Activity Score using 10 joints, CI: Confidence interval, IMD: Index of multiple deprivation, CHAQ: Childhood Health Assessment Questionnaire, ESR: Erythrocyte sedimentation rate, PGA: Physician's global assessment, PGE: Parental global evaluation, sDMARD: synthetic disease-modifying anti-rheumatic drug.

### 6.4.6   Discussion

The burden of disease in JIA remains high. Although the majority of CYP will achieve a single instance of CID within the first three years (up to 80% in oligoarthritis), fewer than 50% will achieve remission within this time frame. Therefore, the disease course in JIA can be expected to exhibit periods of CID and relapse in the majority of cases.

Moving toward precision medicine would allow each patient to receive more personalised treatment, tailored to their own characteristics and prognosis. In order to personalise or stratify care, factors associated with this target state are required. In JIA, a potential target is remission [152]. However, it has been shown that depending on how it is defined, different groups of CYP, with different long-term outcomes, will be classified as having achieved remission [398,411]. The current study reported few clinical or demographic predictors of remission, regardless of definition, based on the assessment at the first presentation to paediatric rheumatology. However, there were stronger associations between changes in disease over the first year and later achievement of remission within the first three years following diagnosis.

At initial presentation to paediatric rheumatology, different treatments are suggested for JIA based on the guidelines available [108,414]. In the UK, the NHS treatment pathway (2015) bases main therapeutic decisions, such as starting MTX, on ILAR category only in the first instance, with further recommendations only after initial therapies have failed [108]. For CYP, excluding those with systemic or active sacroiliac disease, the American College of Rheumatology (ACR) guidelines (2011) also base similar treatment decisions on whether the CYP has oligoarthritis or polyarthritis; however, an additional level of poor prognostic factors has also been built in to help guide the timing of MTX introduction [107]. It has been well-established that CYP with oligoarthritis are more likely to achieve remission than those with polyarthritis [409,413,415] corroborated in the current study. Thus, disease category is a clear marker of prognosis, as taken into account in both ACR and UK NHS treatment strategies [107,108]. However, the additional markers of disease activity and prognosis taken into account in the ACR guidelines have not been consistently associated with remission in JIA [413] and were consistently not associated with remission in the current study and therefore, it is unclear to what extent these additional decision aids will make on patient outcomes.

In addition to ILAR category, the current study found only one consistent factor associated with remission using Wallace's preliminary criteria: older age at initial presentation. Although this finding corroborates a study by Oliveira-Ramos et al. in a population of 426

adults with JIA for at least five years [263], these results conflict with results from a large inception cohort [273] and a smaller retrospective study [272]. However, both of the latter studies used a modified version of the Wallace's preliminary criteria which excluded acute phase reactants and the retrospective study additionally excluded the PGA, making these studies difficult to compare. Age was not associated with remission if defined using cJADAS10, which may indicate that age may be associated with a remission definition which does not include a patient subjective assessment.

Several patient-reported outcomes at initial presentation were associated with remission using the cJADAS10 in univariable models. However, once adjusting for other factors, these were no longer significant. However, socioeconomic deprivation level remained associated with remission, with those from more deprived areas less likely to achieve remission. This may reflect any number of factors not directly measured in the current study, including diet, exercise or smoking exposure [75,416] or factors directly related to their health or condition, such as health literacy or adherence to medications [285,417]. A previous study in this cohort has reported lower levels of functional ability, wellbeing and psychosocial health and higher levels of pain in those with lower socioeconomic statuses [285]. The finding of an association between socioeconomic deprivation and remission using the cJADAS10, but not Wallace's preliminary criteria, is therefore likely associated with the wellbeing rather than inflammatory components of the cJADAS10. However, no study external to the CAPS population has assessed the association between any indices of deprivation and remission in JIA, thus corroborative evidence is needed.

Few previous studies have associated factors following initial presentation with future remission achievement. Those that have, generally associated static disease activity variables, such as active joint counts, PGA scores, CHAQ or previous episodes of CID or remission, with longer-term remission [257,281,288]. The current study explored the degree of improvement over the first year of disease. Greater improvements in the signs and symptoms of JIA were associated with later remission using both definitions. This reinforces the concept of a 'window of opportunity' for the treatment of JIA [290,291]. However, symptom duration to initial presentation was not associated with remission across all models. With the introduction of biologic therapies for JIA and the concept of early aggressive treatment strategies, patients can be targeted with csDMARD and biologics early following initial presentation to paediatric rheumatology. The median symptom duration at baseline for patients in the study was six months and within the year following initial presentation, the majority of patients had accessed steroid therapy, with a majority of patients with polyarthritis having been prescribed a csDMARD and 22% a

biologic therapy. These early treatments may therefore have lessened any association between delay to care and remission.

Depending on ILAR category, greater improvements in certain factors were associated with remission using Wallace's preliminary criteria. In both categories studied, greater improvements in PGA and PGE scores were associated with remission. However, greater improvements in active joint counts and ESR were associated with remission only in oligoarthritis, with greater improvements in limited joints counts associated with remission only in polyarthritis. The discordance associated with active joint counts may stem from a difference in remission achievement between patients with extended and persistent oligoarthritis. In a sensitivity analysis, when patients with extended oligoarthritis were excluded from the oligoarticular group, greater improvements in active joints counts remained associated with remission using the cJADAS10 (OR: 0.6, 95% CI 0.4, 1.0, p=0.041) but not Wallace's preliminary criteria (p=0.102, data not shown). However, the differences between ESR and limited joint counts between ILAR categories may reflect the need for monitoring different factors when treating oligoarthritis versus polyarthritis.

The current study benefitted from a large, multicentre inception cohort of patients with JIA. Longitudinal data collection allowed the inclusion of multiple time points within which to assess the achievement of remission. Results gained are therefore likely generalisable to the general population of patients with the JIA categories investigated. The CAPS cohort collected a variety of clinical and non-clinical factors, including socioeconomic status that had previously been overlooked for associations with remission. Although there were missing data, as would be expected in a study of this nature, multiple imputation was utilised to account for missing covariate data and incorporated clinically relevant assumptions for missing outcome data.

Unfortunately, too few patients with extended oligoarthritis or RF-positive polyarthritis were present to be able to stratify or control further for these two factors. In addition, certain factors that may be associated with remission were not investigated, such as ANA positivity. Limitations in the number of CYP achieving remission limited the number of exploratory variables incorporated in the analyses. Since ANA has frequently been reported to not associate with remission [6,269,284] and was missing in over 60% of CYP in this cohort, this factor was not explored. It was also not possible to explore the impact of individual joint patterns do to the high number of possible combinations in relation to the number of outcomes observed. Similarly, the ACR 2011 provisional criteria for CID in JIA [185] could not be assessed to a lack of data on morning stiffness. The similarity of this

measure to Wallace's preliminary criteria would likely produce similar results. Finally, data were collected annually and remission assumed where two consecutive annual time-points showed CID. It is possible that disease may have flared between follow-ups and thus a proportion of CYP may have been misclassified as 'in remission'. However, this would have resulted in an attenuation of point estimates and thus the true values may be at least as large as those presented.

### 6.4.7　Conclusion

In an inception cohort of patients with JIA, there are few clinical or patient-reported factors measured at initial presentation which are associated with later achievement of remission. Greater remission achievement was seen among those who improved the most over the first year following initial presentation, reinforcing the importance of early disease control. Based on how remission was defined, however, improvements in different factors associated with remission. Therefore, the definition of the treatment target is important for further research intro stratified treatment approaches.

### 6.4.8　Acknowledgements and Affiliations

### 6.4.9　Competing Interests

The authors declare no conflicts of interest.

### 6.4.10  Supplementary Materials

Missing outcome data were managed in this analysis as under previously constructed assumptions for data regarded missing not at random [398]. The previous assumptions were based on the following reasons for drop-out from the CAPS study: i) discharged 'well', ii) discharged due to repeat non-attendance, iii) discharged due to moving clinic iv) discharge for other reason. In addition, further missing data were evident where patients were v) lost to follow-up and vi) presented to clinical appointments but had incomplete outcome data.

Following baseline analyses of disease and patient-reported factors across groups with different missingness types in addition to consultations with paediatric and adolescent rheumatologists, the following assumptions were made: For groups i), ii), v) and iii) if definitively transferred to adult practice or aged $\geq 14.5$ years at discharge, CYP were assumed to be in CID according to both Wallace's preliminary criteria and the cJADAS10. In addition, if patients presented to clinical appointments but had missing acute-phase reactants (ESR or CRP), these values were assumed to be normal. For group iii) if aged $<14.5$ at discharge, iv) and vi) if missing data other than acute phase reactants, missing data were assumed to be missing at random. A further assumption was placed regarding CYP that skipped clinical appointments and returned prior to the three year follow-up. These CYP were assumed to be similar to those who had repeatedly failed to present or those lost-to-follow-up: for the appointments that they had skipped, they were assumed to have fulfilled the CID criteria for both Wallace's preliminary criteria and the cJADAS10.
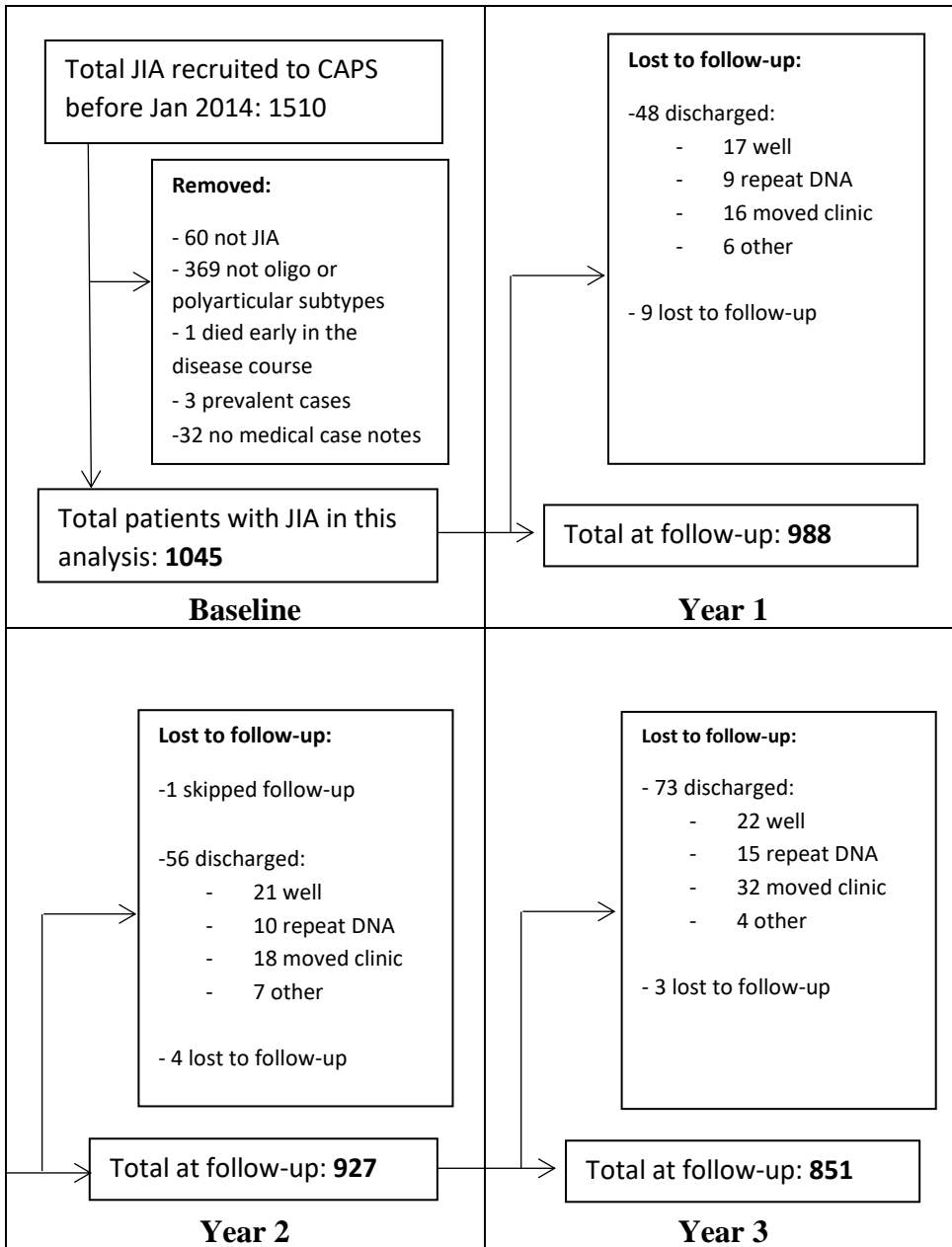
**Supplementary Figure 2.** Patient flow through the study

# Chapter 7

# Discussion

*This thesis primarily focuses around the achievement of remission in patients with JIA. The frequency, long-term outcomes following and factors associated with remission have been reported, often differing by remission definition. This final discussion chapter will expand on the clinical and research implications of the findings presented in this thesis. This will include further discussion of the limitations and biases inherent in observational data and how these may have affected the results observed. Clinical implications and potential future research in this area are discussed.*

# 7 DISCUSSION

In an ideal world, the aim of treating JIA would be a cure, but until that becomes a feasible and realistic outcome, the current aim of treating JIA is remission [152]. This thesis set out to understand remission in JIA: its frequency, outcomes following its achievement and factors associated with its achievement. This would allow the understanding of i) how commonly it is achieved ii) whether it leads to better physician and/or patient-reported outcomes compared with active disease and iii) which CYP might be more or less likely to achieve remission. The answers to these research questions could both facilitate communication with patients/families and inform treatment decisions. Whilst, at first, these seemed like straightforward objectives, it quickly became clear that the ability to classify CYP with JIA into remission and active disease states was challenged by the presence of multiple recently proposed composite outcome definitions. Each had different components, including the number of measures of disease activity included in the assessment as well as whether or not a patient/parent's assessment of the disease was taken into account. These differences challenged the concept of what is meant by 'disease remission'.

This thesis, broadly, has found that despite advances in treatment, the disease burden in JIA is high, with a majority of children not achieving remission over the first 3 years of disease (Papers 1 to 4). As suspected, the different proposed definitions for CID and remission did not identify the same groups of children (Paper 2) and these children then had different longer term outcomes (Paper 3). Unfortunately, few factors at initial presentation were associated with remission but improvements in the first year following diagnosis do lead to greater odds of future remission (Paper 4). Additionally, if inflammation is controlled but CYP do not feel better, as evidenced by persistently high scores on the PGE, their long term outcomes, especially in terms of functional ability and HRQoL, are no different from those who do not achieve early remission, although their joint damage is stopped (Paper 3).

## 7.1 What is Remission?

The research in this thesis has challenged fundamentally what is meant by remission in JIA. It is commonly discussed as the optimal target or outcome of treatment, but the findings in this thesis suggest it may mean different things to different people. Does it mean a complete absence of inflammation or evidence of the underlying disease process in JIA, a complete absence of symptoms or outward signs of the disease, or both?

Importantly, to facilitate clinical care and research, this must be a state which one can measure consistently between CYP and research studies.

### 7.1.1    Which Measures Could be Included in Remission Criteria?

To define remission, there are multiple physician and patient-reported outcome measures, including clinical examinations, results of blood tests or patient reported factors, which could be assessed. There are further measures not commonly used in clinical practice such as imaging studies or other biomarkers.  As a single test for remission in JIA does not exist, we must rely on these measures, either on their own or as part of composite measures, to make assessments about remission. Since composite measures cannot feasibly include all possible measures of disease activity and its impact, subsets have been devised with an aim of capturing multiple key elements of this construct [232].  An important question regards which measures should be included in such a subset to best capture remission.

The current thesis suggested that the main factor driving disagreement between existing remission criteria was the inclusion or exclusion of patient-reported items. When developing Wallace's preliminary criteria, the defined states included 'clinically inactive disease' and 'clinical remission'. As suggested in the names, these criteria focused only on disease activity measured in a *clinical* setting, with the investigators explicitly allowing for pain on motion or joint tenderness in CYP achieving their remission definition. The concept of pain in the absence of inflammation is suggested to constitute remission if *"attributable to arthritis that is now considered inactive"*. Therefore these investigators allowed children to have persistent symptoms of disease as long as the inflammation was not detectable. In direct opposition, the JADAS cut-off developers specifically aimed to capture a disease state including good wellbeing, and therefore a lack of pain, to include the view of the patient as to the effects of their disease.

The discordance between physician global scores of disease and parental scores of wellbeing has been well documented. The former tend to correlate better with measures of inflammation, such as joint counts and CRP, with parental scores of wellbeing tending to correlate better with pain and function [160,195,418]. These findings are to be expected given that one can only comment on what one observes or experiences. Drivers of discordance again include pain and poor function in CYP considered in 'non-active disease' by physicians and not by parents [391]. These suggest that the impact of disease is considered fundamental to 'disease remission' for parents but not physicians, whose main aim may be to target inflammation using pharmaceutical interventions. To target patient wellbeing,

several complementary interventions, such as physiotherapy, occupational therapy and psychological services, may also be needed.

### 7.1.2 Are Composite Measures of Remission Helpful?

An alternative to using composite criteria for remission would be to assess individual key features of disease and its impact. This would allow the quantification of the absence of signs versus symptoms of disease and may facilitate referrals to allied healthcare professionals where symptoms are independent of current inflammation. However, the use of single outcome measures does not give an overall picture of disease in a heterogeneous condition such as JIA [232], with the current thesis demonstrating 85% discordance in groups of CYP identified by single measures: active joint counts, physician and parent global assessments. It would be challenging to communicate the resolution of the disease to patients and to compare this resolution across research studies in larger cohorts of patients. In addition, having multiple primary end-points in clinical trials is methodologically challenging and so may be unfeasible in a research setting [232].

There is also a risk that splitting signs and symptoms of disease may facilitate further the focus of rheumatologists on inflammation. There is a growing movement to place the patient at the centre of their own treatment [419,420] with shared decision making between physicians and patients key in both target and treatment selection in T2T strategies [152]. Treating toward a state which is not acceptable to patients as a primary goal does not fall within this paradigm. However, targeting disease states including high wellbeing likely requires the piloting and trialling of complementary strategies with regard to how to incorporate escalating anti-rheumatic therapies with increasing access to, and interventions from, other allied health services.

Whilst using single outcome measures comes with the challenges described, it is likely paramount that both single and composite scores are accounted for in clinical practice. T2T strategies are beginning to be considered for CYP with JIA [152]. If a composite measure of disease activity, such as the JADAS, were used in isolation as a basis for anti-rheumatic medication escalation, many patients may be over-treated based on the persistence of non-inflammatory symptoms. These patients would include those in remission according to Wallace's preliminary criteria but not the cJADAS, as identified in this thesis. Therefore, a single score should not be implemented without context when treating JIA to target. Rather, a single score such as the JADAS would facilitate the agreement of physicians and parents that both signs and symptoms of JIA have, or have not been, resolved. If remission has not been reached, further information regarding the

specific persistent signs or symptoms should be explored before treatment decisions are made.

### 7.1.3   Are Current Definitions of Remission Fit for Purpose?

Until more is understood about JIA, and the ways in which disease can be measured, it is likely that both the Wallace Preliminary Criteria and the JADAS cut-offs will continue to be used. Therefore, the current strengths and limitations of these criteria should be considered. Wallace's preliminary criteria necessitate all components to have the best score possible or be within normal range in order to be classified in CID to confirm the absence of disease activity; however, it may not be feasible to achieve a score of zero or have 'normal' results in every aspect of the remission criteria. In particular, it may be difficult for physicians to score zero on the PGA. Part of this is technical. On paper-based forms, even if a score of zero is desired, a mark may be misplaced at two or three millimetres from the end of the scale [421]. But there is also evidence that  clinicians may not mark at exactly zero even when they feel there are no current signs of inflammatory disease [201]. Drivers of PGA score variability in patients who had achieved CID on all ACR preliminary criteria components, excluding the PGA, included the presence of pain, "questionable" temporomandibular involvement, limited range of motion in joints, the presence of any morning stiffness and previous episodes of uveitis activity [201]. One option would be to allow a score <0.5cm or <1cm to indicate remission. There has been no MCID defined for the 10cm VAS PGA, however, MCID on a 21-numbered VAS (range 0-10cm) has been reported at between 1.3cm and 1.4cm, depending on whether the CYP had improved or worsened [421]. Thus, the two or three millimetre scores seen in this thesis among children who otherwise scored zero across all components likely do not represent a clinically important difference from zero. Thus, through error and/or end-point aversion, a CYP may never be observed to reach remission according to Wallace's preliminary criteria, regardless of current disease status. In addition, certain items within the criteria set are not currently routinely collected, such as ESR [198].  The misclassification of, and non-applicability to all, CYP with JIA likely means that, in its current form, Wallace's preliminary criteria may not be the best choice as a marker of remission or for use as a treatment target.

An alternative to the strict 'best score only' method of Wallace's preliminary criteria, the JADAS scores allow CYP to have achieved remission if scoring below a certain cut-point. This has the advantages of avoiding errors and limiting end-point aversion previously discussed. No great differences in disease activity were observed in this thesis for patients

fulfilling JADAS but not Wallace's preliminary criteria and those who fulfilled both. Therefore, using a cut-point rather than an absolute absence of disease does not overestimate remission. This was further demonstrated in the equivalent lack of limited joints as a measure of joint damage over five years following the achievement of remission according to the cJADAS or Wallace's preliminary criteria. In addition, fewer elements, which can all be collected routinely in all patients with JIA, aid the feasibility of the cJADAS for implementation into clinical practice. When the remission definitions were applied to CAPS, the greatest number of CYP that could be classified and the narrowest limits for extreme scenarios without having to impute data was evident for the cJADAS. In addition, the capture by remission criteria of two different features of JIA, inflammation and its impact, has been demonstrated in this thesis to identify different groups of CYP with different long-term outcomes. Those with high wellbeing in addition to no inflammation had the best outcomes in terms of function, quality of life and joint limitation. These findings favour the incorporation of both physician and parent-reported factors into composite remission criteria. However, this applicability is limited to patients with oligoarticular or RF-negative/positive polyarticular disease who do not experience uveitis. Further development of criteria will be needed for those CYP within other ILAR criteria or those with other extra-articular features of disease not explicitly captured by the cJADAS.

## 7.2 Thesis Strengths

The largest strength of this thesis was the study population: CAPS. CAPS recruits from multiple hospital locations, the seven selected being across England and Scotland, with one hospital nearing the Welsh border. Coverage of the UK is therefore wide, with the exception of Northern Ireland. For a rare disease, CAPS has also recruited in relatively large numbers; it is the largest inception cohort of JIA globally, having recruited over 1600 patients [297]. This allows greater statistical power when analysing CAPS data, even for rarer outcomes such as remission. By recruiting many patients from multiple hospitals, CAPS patients therefore reflect a collection of CYP whose exposures and disease features generalise well to other CYP with JIA who were not recruited to the study. In addition, since all patients had access to contemporary treatments, CAPS is well-placed to study the current achievement and outcomes following remission in contemporary CYP with JIA.

Whilst many of the analyses presented in this thesis were limited to CYP with oligoarthritis or polyarthritis ILAR categories, the collection of data by CAPS from patients with the rarer ILAR categories allowed this thesis to also explore their frequencies

of remission. Although certain features of their disease were not included in the remission definitions, the second paper could estimate the frequency of a range of single and composite outcomes.

All patients recruited to CAPS were followed from their first appointment with paediatric rheumatology. This inception cohort design minimised selection bias compared with prevalence cohorts, where left censorship may limit the inclusion of certain CYP, particularly those with less severe disease or who achieve remission early in disease and are discharged from rheumatology clinics. By including all patients, and having information regarding reasons for study attrition, this thesis was able to infer clinically plausible disease statuses for these CYP. Their exclusion from prevalence studies may have underestimated the achievement of remission in previous reports. Having recruited CYP from initial presentation also allowed changes to disease activity in the early stages of treatment to be analysed, when the greatest change in disease is often observed.

CAPS collected a vast array of data both from clinical records and through patient questionnaires. Since no additional data are requested and additional pressure is not put upon physicians assessing patients in CAPS-recruiting hospitals, the incomplete data observed therefore represents real-world availability of data. This allowed the broad assessment of feasibility of the various composite outcome criteria in clinical settings and directed the analyses presented in this thesis to only routinely collected variables. This routine data collection incorporated all items of Wallace's preliminary criteria, the JADAS and cJADAS and therefore this thesis was able to assess remission across multiple definitions. In addition, the variety of data collected allowed the analysis of multiple physician and patient-reported items for use as outcomes following the achievement of remission. Further, the number of items explored as potential predictors of remission was not limited by the number of variables collected in CAPS. Variables were selected based on clinical relevance and the amounts of available data.

The long-term follow-up in CAPS allowed longitudinal data analysis. Previous studies had not explored long-term outcomes following the fulfilment of remission or MDA according to those studied in this thesis. Having data available to five years allowed both short and long-term outcomes to be explored.

Although these strengths of CAPS allowed the research questions in this thesis to be addressed, certain limitations were evident, with the largest being missing data. In addition, the definitions of remission themselves limited the amount of CAPS data that could be used for study.

### 7.3 Thesis Limitations

#### 7.3.1 Data Quality within CAPS

*Defining Remission using CAPS Data*

Although the CAPS cohort was designed to assess and predict outcomes in CYP with JIA, it was not specifically designed to study remission using the criteria studied in this thesis, which did not exist at the outset of the cohort in 2001 and a simple question "Is this patient in remission?" was not included. Since the JADAS and cJADAS are formed from subsets of the JIA COVs, these were calculable. However, certain components of the other remission criteria, such as morning stiffness for the ACR provisional criteria [185], have not been collected and the achievement of others, such as absent systemic symptoms or uveitis had to be inferred from other questions within CAPS. Since paediatric rheumatologists do not directly assess uveitis, it is understood that CAPS research nurses gained this information from ophthalmology records in the CYP's medical notes. Using this information, research nurses then had to determine the presence or absence of either acute or chronic uveitis for each follow-up. Therefore there may have been some misclassification of uveitis activity in either direction. These challenges highlight the difficulty in managing and recording outcomes in a complex disease which is not completely assessable at the point of contact with a single paediatric rheumatologist.

*Defining Long Term Outcomes*

The long-term outcomes assessed following the achievement of CID and MDA were intended to capture joint damage, pain, functional ability and HRQoL.

A lack of joints with limited range of motion was used as a proxy for joint damage in the CAPS cohort. Although a selection of patients would have undergone imaging analyses to assess joint damage, perhaps as a more objective measure of joint damage, these data were limited. Joint limitation also may be due to factors other than bony erosion in JIA, such as muscle contracture in chronically inflamed joints. In the future, linkage of CAPS to the England Hospital Episode Statistics or the National Joint Register may provide further information on these outcomes, such as joint surgery.

Limitations in the current understanding of the multifactorial nature of pain challenged which outcome was assessed following the achievement of MDA versus CID. Chronic pain appears to persist in some patients only when inflammation is active. However, in other patients, this pain persists in the absence of inflammation [422,423]. In young people with JIA, it is not currently possible to distinguish between pain related to, or not related

to, inflammation. When assessing long-term outcomes following the achievement of CID, ideally inflammatory and non-inflammatory pain would have been modelled as separate outcomes. However, it currently remains unclear what are the drivers of pain in children with no apparent inflammation.

## The Use of Proxies in Paediatric Research

A further possible limitation of the study is that many outcome measures, such as the CHAQ, CHQ and PGE, are usually completed by a guardian or parent for young children and reflect their opinion on how the disease affects their child. For older children and young adults, many will then switch to completing the measure themselves. For example, the CHAQ is completed by the child's guardian early in life (before age 11) and then, in most but not all cases, by the young person themselves after that. Therefore, over time, the CHAQ could be represented by two different parties if the CYP turned 11 over the course of follow-up. However, a previous study in the CAPS cohort has demonstrated high agreement between proxy-reported and CYP-reported CHAQ scores where 85% scores were similarly classified within 0.25 points [203]. A second study of UK adolescents with JIA reported proxies to significantly overestimate functional disability compared with patients by a mean of 0.1 points (SD 0.5) [424]; however, given that the MCID between CHAQ scores is estimated to lie between 0.13 and 0.19 [425], this may not be a clinically relevant difference. Therefore, whilst patient and proxy scores were used interchangeably in this thesis, this likely did not impact the results in a clinically meaningful manner.

## Interval versus Continuous Data Collection

As part of CAPS, data were extracted on an annual basis with temporally closest data items recorded in the medical record related to each annual follow-up. It is known that JIA is a disease of remission and relapse [181,238], with many clinical studies relying on annual or bi-annual data as a basis for plotting disease trajectories [297]. This lack of granularity, both in the frequency of appointments in standard clinical practice and the collection of data by research studies, limits the observation of the full spectrum of the signs and symptoms of JIA over time.

To implement the truest form of remission according to the criteria used in this thesis, which do require a period of observation without disease activity, disease activity must be monitored more frequently, if not daily, to determine if CID has indeed been maintained. This is clearly an unfeasible undertaking if requiring continuous physician's assessments and certain assumptions must be placed about the length of time a CYP can be assumed to

have maintained CID. For research, the most pragmatic approach to classifying remission could be the maintenance of CID for a year given the most frequent windows of data extraction, that may be more or less frequent than this window in practice. As part of CAPS, the most frequent data extraction time points were annual, designed to capture key changes in disease over time but minimise the burden of data collection. Therefore, to be assumed to have reached remission, CYP had to have been in CID for at least two consecutive follow-up points. Under this assumption, some CYP will have been misclassified as 'in remission' when, in reality, their disease flared in intermediate non-observed time. Conversely, a proportion of CYP will have experienced CID for a year that did not coincide with two annual follow-ups. This misclassification may have over or underestimated the number of children attaining remission and may have attenuated the associations between potential factors and remission in the final paper. Thus, associations can be assumed at least as large as those reported.

### 7.3.2   Missing Data within CAPS

A substantial amount of missing data was found in the CAPS database. This occurred both in terms of missing data items at otherwise completed follow-ups and attrition from the study.

*Missing Data Items*

When attending clinic appointments, all patient data required for research may not be measured or recorded. There may be a general pattern as to why these data are incomplete. If so, certain assumptions about the values of these missing data can be made. In the analyses of CAPS data, assumptions were placed regarding the disease activity states of CYP who had presented to clinic appointments but had incomplete data.

For CYP who presented to clinic but had incomplete data, the probability that some of these data were missing likely depended on other captured factors. These data could therefore be imputed under standard methods of multiple imputation assuming data were MAR. However, for a subset of variables, the probability of their being missing was likely related to their values. This was the case for acute phase reactants, where collection is only indicated in a subset of CYP with more severe disease [198]. The absence of these values when a clinic appointment had been attended was, therefore, indicative of mild or remission-like disease. For additional variables such as AJC or PGA scores, missing values when clinic appointments had been attended was unlikely to associate with disease activity.

The approach taken, setting certain missing values to values consistent with remission, was undertaken based on a combination of published evidence, previous data in CAPS and expert opinion. Although more clinically plausible than imputing data based on a MAR mechanism, the imputation of a single value likely resulted in narrower confidence intervals, an overestimation of remission and attenuation of associations with remission.

### *Missing Participants Following Study Attrition*

Patients may not have presented to clinic appointments for various reasons, including having been discharged or lost to follow-up in CAPS. Reasons for leaving the study, or informative drop-out, were available in the majority of cases, with only approximately 3% of patients lost-to-follow-up for unknown reasons within the first five years following recruitment. Where patients had been discharged, the reasons for discharge included those 1) Discharged 'well', 2) Discharged due to repeat non-attendance, 3) Transferred to another paediatric rheumatology clinic 4) Transferred to adult care and 5) Moved house or unknown reason for discharge.

There are likely no consistent associations between moving house, most likely due to reasons associated with the wider family, and the values of missing disease variables. Missing data from CYP discharged for this reason were therefore imputed assuming data MAR. However, where CYP had been discharged 'well', this is a clear indication that these CYP were highly likely to have achieved remission. These CYPs were assumed to be in remission and symptom free according to both Wallace's preliminary criteria and JADAS/cJADAS scores although it is unclear whether they would have been formally classified as such by the validated remission criteria.

Through discussions with paediatric and adolescent rheumatologists, it was discussed that adolescents are unlikely to be transferred from paediatric to adult practice until their disease activity has been controlled, with much experience from post-transfer practices focusing on daily living, such as occupational and sexual health. It was therefore deemed likely that these young people had achieved a state of disease remission upon transfer. Disease parameters in these young people were therefore assumed to fulfil the various remission criteria. However, pragmatically, a young person with active disease cannot be retained by paediatric rheumatology services indefinitely. The potential misclassification of disease activity in these young people may have resulted in an overestimation of the frequency of remission. However, these patients comprised fewer than 1% of the cohort at one year. Therefore, any overestimation was likely minimal.

Finally, there is published evidence to suggest that CYP who do not present to clinical appointments were more likely to have low or no disease activity than those who do attend their appointments [250,351]. One study reported better function in participants lost to follow-up than those remaining in the study (78% HAQ=0 in those lost-to-follow-up versus 53% HAQ=0 in those presenting to clinical appointments). Of course, the opposite may be true in some children, where the reasons they do not attend clinics may correlate with other factors, such as non-adherence to medication and therefore this assumption may not have rang true in all children. Again, low levels of disease which would not fulfil remission criteria also cannot be ruled out. However, multiple imputation of complete missing datasets in children with known reasons for leaving the study may also have overestimated the rates of CID, especially if individual components were imputed rather than the entire disease state.

### 7.3.3   External Validity of Results

The JIA population recruited to CAPS is highly representative of other international cohorts of JIA in terms of demographics, ILAR category distributions and other features of disease [5,27,275]. Therefore, the results may be generalisable at least to the types of patients that enrolled in other observational studies.

Within the UK, CAPS recruitment centres have good geographic coverage over England and Scotland from paediatric and adolescent rheumatology centres. It is unknown how well these results generalise to patients who initially present to adult rheumatology in late adolescence or early adulthood. Further work is needed to assess outcomes following, and factors associated with, remission in these older patients with JIA. However, within those who initially present to paediatric rheumatology with JIA, it was not possible to collect data regarding differences between those who did and did not enrol in the study. The exact incidence of JIA in the participating centres is unknown and therefore it is not known how many children were not approached to participate or who was approached and declined to participate. It is therefore unclear exactly how representative CYP enrolled to CAPS are of the general UK JIA population. There are differences in socioeconomic status and representation of ethnic minorities between the CAPS population and the general UK population. These may be driven by higher susceptibility to disease for those with lower socioeconomic status and white ethnicities, or by the inclusion criteria for enrolment to the study. It is also known that over the period of CAPS recruitment, there were periods where no recruiting nurse was available in some centres due to logistical reasons and therefore,

some of the children missing in CAPS would be MCAR, and therefore no bias would have been introduced.

## *Barriers in Presenting to Paediatric Rheumatology Tertiary Care Centres*

Patients that live in remote areas may not have ready access to a local hospital, let alone specialists in paediatric rheumatology. All centres in CAPS were based in large teaching hospitals in major UK cities. Travelling to specialist hospitals from remote areas may only be feasible in certain circumstances and has been previously identified as a barrier to recruitment for research across both developing and developed countries including the UK [302,303,305,426]. CYP whose guardians, for example, have no, or little, access to transport, who cannot afford transport or who do not have the time to travel to distant hospitals may have lesser access to specialist paediatric rheumatology care. For CYP who reside closer to specialist hospitals, additional barriers to presenting to clinical appointments may still exist. In addition to the reasons previously stated, CYP with families who are more health-literate likely present to clinical appointments more readily that those from families where health literacy is lower [302,303,427], even when their signs and symptoms of disease may be comparable. Although IMD was explored in the CAPS subgroups selected for analyses, no direct comparison could be made regarding locations of or socioeconomic standing of participants compared with other families with JIA not enrolled to CAPS. Overall, compared with the general UK population, greater socioeconomic deprivation was overrepresented in the CAPS population. This may reflect that for CYP with JIA, socioeconomic status may not represent a great barrier to care, particularly in light of the universal healthcare system in the UK. However, this may alternatively represent a greater susceptibility to JIA, or, as has been previously reported from this cohort, worse symptoms in CYP with lower SES [285], potentially facilitating greater seeking of care in families from more deprived areas.

## *Barriers to Enrolling Eligible Patients Presenting to Clinical Appointments*

The percentage of CYP (0-15 years) with ethnic minority backgrounds is marginally smaller in CAPS (10% non-white) than in the general population in England and Wales (16% non-white in the 2009 UK census, no paediatric-specific ethnicity data available after this point) [428] and Scotland (CAPS: 6%, Scottish Census 2011: 9% [429]). This could potentially be attributed to the local ethnic diversities of populations surrounding CAPS hospitals or differences in susceptibility to JIA among different ethnicities [60,80,81]. Alternate explanations could include the non-recruitment of families who do not understand English language with enough fluency to enable informed consent, or who do not understand the

explanation of the study provided [303,304]. Although translators can be provided, if there is doubt that the patient or family does not fully understand explanations provided, informed consent cannot be assumed. In some cases, families may have learning difficulties that preclude the process of informed consent to proceed ethically. There may also be a presence of 'gatekeepers' in healthcare professionals recruiting to the study, who do not approach minority patients [303]. In these cases, potential participants are not afforded an opportunity to understand and consent to the study. Finally, certain groups of patients may not want to participate in research, for either cultural or personal reasons [302,303,305]. The clinical implication of not including potentially eligible patients is a decrease in the generalisability of the results gained. These results may be particularly important for these 'hard to reach' patient groups, with whom limited research is able to be conducted, who therefore experience reduced benefit from research outputs [303]. Limitations in generalisability are an inevitable consequence of not recruiting every single person with the disease of interest and as a large, multicentre inception cohort, CAPS is near to optimal.

### 7.3.4 Applicability of CID and Remission Definitions across the Spectrum of JIA Categories

The first and second paper in this thesis focused on quantifying CID and remission across all ILAR categories of JIA. However, the definitions employed were not designed for use in all categories and do not capture key extra-articular disease features, particularly of the less common forms of JIA [165,168,186]. In adult-onset arthritis, similar disease constructs to the rarer ILAR categories are classified as distinctly different diseases to RA: adult-onset Still's disease (similar to systemic JIA), ankylosing spondylitis (similar to enthesitis-related JIA) and psoriatic arthritis (similar to psoriatic JIA) [430]. These are not only characterised by different clinical manifestations, but also different underlying susceptibility and disease pathways, including different responses to therapies [430]. Although remission is often assessed in entire cohorts including all JIA categories, they represent groups of CYP with distinct genetic features accompanied by specific extra-articular features of disease [1,431,432]. One question is the importance of including or excluding activity in disease features that are not common to all children.

*Uveitis and Systemic Features across ILAR Categories*

Uveitis and systemic features both form part of the remission criteria according to Wallace's preliminary criteria but not the JADAS scores [186,237,240]. Although systemic features are not explicitly included in many definitions of remission, it is possible that

these features are taken into account when scoring the PGA and PGE although this is currently unknown, with no specific research into this area. However, when multiple definitions of remission, variably including PGA, PGE scores and systemic features, were applied to the CAPS cohort, fewer CYP with systemic JIA were observed to be in remission when systemic features were included in the remission criteria more explicitly. This lead to approximately double the proportion of patients with systemic JIA being classified in remission according to the JADAS (37%) and cJADAS (38%) criteria compared with Wallace's preliminary criteria (19%). Therefore, the JADAS and cJADAS overestimate the number of CYP with systemic JIA in remission, or suggest that systemic features are not taken into account when assessing the PGE and PGA. Similarly, the JADAS scores will overestimate remission in CYP with uveitis. Given the asymptomatic nature of uveitis in JIA[151], associations with long-term outcomes such as joint limitations, function and pain were likely unaffected. However, given the short-term severe consequences of uveitis activity [22], any T2T strategy targeting JADAS remission would require the incorporation of uveitis.

*Enthesitis-related and Psoriatic JIA*

Enthesitis and psoriasis are not explicitly addressed in any of the remission criteria described in this thesis. As previously stated for systemic JIA and uveitis, the disease features may be captured to some extent by the PGA and PGE, with psoriasis activity being a driver of discordant PGA scores in patients with low disease activity [201]. However, to truly capture a resolution of enthesitis and psoriatic signs and symptoms of JIA, these features must be explicitly incorporated into remission criteria. The estimates of CID and remission in both the systematic review and those estimated in the CAPS cohort may therefore overestimate the frequency of these states both in the entire cohort and for these ILAR categories specifically.

Whilst CYP with enthesitis-related JIA and psoriatic JIA may have similar long-term joint limitations to those with oligo/polyarthritis, these categories were excluded from the analyses in Paper 3. CYP with enthesitis-related or psoriatic JIA may experience distinct types of pain additional to that associated purely with joint involvement, such as inflammatory spinal pain [433]. This may impact the scoring of functional ability, such as items requiring turning one's head or bending down. Therefore, modelling long-term outcomes for CYP across all ILAR categories could have resulted in modelling distinctly different disease processes within the same models, confusing the clinical message regarding which remission state is optimal in terms of long-term outcome. For assessing factors associated with remission, CYP with enthesitis-related, psoriatic and

undifferentiated arthritis were again excluded from the analysis. Whilst the results might generalise to predictors of their joint activity, the variables identified may not associate with the resolution of extra-articular manifestations of JIA. Further work will need to identify predictors of the resolution of these disease features, potentially within revised definitions of remission.

## *Oligoarticular, RF-negative Polyarticular and RF-positive Polyarticular JIA*

The final two analyses in this thesis only included CYP with oligoarthritis, RF-negative polyarthritis and RF-positive polyarthritis. Although many other features of disease can be evident for CYP with these disease categories, the primary feature is joint inflammation [1]. By including active joint counts in addition to global assessments of disease, Wallace's preliminary criteria and the JADAS may therefore accurately capture a lack of inflammation and good wellbeing in addition to a lack of inflammation in these categories, respectively. Since different remission achievement and different levels of functional ability were evident between oligoarticular and polyarticular JIA, the associations between remission states and long-term outcomes were analysed whilst adjusting for the confounding effect of ILAR category (measured at one year following initial presentation). However, the differences in oligoarticular versus polyarticular JIA in terms of their presentation and how they are treated led to the decision to undertake a stratified analysis when exploring factors associated with remission. In this stratified analysis, however, there may have been similarities in both the presentation and treatment of young people with extended oligoarthritis and those with polyarthritis. By one year following JIA diagnosis, patients with extended oligoarthritis and those with polyarthritis have both experienced inflammation in at least five joints [1]. Since disease onset may pre-date initial presentation to paediatric rheumatology by more than six months, CAPS recruits a limited number of CYP who were diagnosed with extended oligoarthritis at this first appointment (approximately 4% of patients with oligoarthritis at initial presentation). Similar treatment strategies may therefore have been undertaken in CYP with these high numbers of inflamed joints, particularly if not associated with RF-positivity. These similarities in disease may partially explain the similarities in predictors of remission across oligoarthritis and polyarthritis, particularly using the cJADAS10.

In these analyses, both RF-negative and RF-positive polyarticular JIA were combined into a single polyarthritis model when exploring risk factors for remission. Although the primary disease feature in both polyarticular JIA subtypes is the presence of five or greater inflamed joints, these categories are different in terms of both their genetic susceptibility

[434] and long-term outcomes; CYP with RF-positive polyarticular JIA consistently had the poorest outcome in terms of CID and remission of all of the subtypes in the systematic review. However, it was not possible to further adjust the models for ILAR category due to the small numbers of CYP with RF-positive polyarthritis and resulting perfect prediction of outcome with other variables in the imputation models. These low numbers of CYP also precluded a separate model entirely for RF-positive polyarthritis. These factors associated with remission may therefore generalise better to CYP with RF-negative polyarthritis than RF-positive polyarthritis. Further work should explore predictors of remission in RF-positive polyarthritis in larger sample sizes.

## 7.4 Clinical Implications

This PhD has confirmed that the burden of disease activity over the first three to five years of JIA remains high. Thus, expectations that JIA disease activity might 'run its course' or be 'self-limiting' [7] may be unfounded in most CYP. With increasing use of biologic therapies for JIA, this clinical picture of disease may be improving. However, this thesis was not able to disentangle whether changes in therapeutic strategies has resulted in increased CID or remission rates. Since the burden of disease remained high even in this contemporary cohort with access to biologic therapies [5], expectations should be set when managing patients with JIA that remission is unlikely within early years of disease, although improvements in disease are very possible.

Despite a high burden of disease activity for the entire cohort of JIA, there are different prognoses for CYP with different ILAR categories. This burden is particularly high for CYP with RF-positive polyarthritis (<20% CID), with intermediate achievement of CID for those with RF-negative polyarthritis (25% to 31%) and those with oligoarthritis having the most favourable achievement of CID (34% to 43%) at one year. Therefore, expectations of disease outcomes should be set lower for CYP with five or greater active joints at initial presentation and these patients may require targeting with more aggressive treatment strategies.

Although patients with greater numbers of active joints may have poorer prognoses, the absence of active joints did not always coincide with the absence of other disease features. Further features in addition to active joint count therefore drive the assessment of CID. In addition, poor wellbeing can be evident despite a lack of objective measures of inflammation and vice versa. To capture both the inflammatory pathways and the impact of JIA on CYP, both physician and patient/parent input are therefore vital.

Despite discordance between CID definitions, controlling inflammation, regardless of wellbeing, predicts the absence of joint limitations. However, wellbeing is an important predictor of function and HRQoL. Given that inflammation seems to not associate with these outcomes, targeting inflammation may therefore not aid in long-term function if wellbeing isn't also taken into consideration.

Taking a stratified approach to treating JIA, predictors of remission would be most useful at initial presentation to paediatric rheumatology or very early within the treatment pathway, likely before the initiation of anti-rheumatic drugs. Correctly identifying effective treatment pathways would maximise patient benefit in controlling disease at the earliest time point. In addition, the side-effect profiles of many csDMARDs and biologic therapies, such as medically significant infections or anticipatory nausea, can be severe and greatly influence quality of life when experienced [111,435]. All patients receiving these therapies are at risk of adverse events, whether or not they produce a clinically beneficial response to treatment [111,436]. Stratified medicine based on both the probabilities of treatment response in addition to risk of adverse events may therefore be necessary to balance these potential outcomes. However, correctly identifying patients who may not clinically respond to specific therapeutic approaches is a certain step toward minimising the accumulation of these adverse events, including drug toxicity, from unnecessary therapies.

There are also great economic benefits to early effective and safe therapeutic strategies. Biological therapies are the most expensive pharmaceuticals available on the UK NHS [437], with the most commonly prescribed first-line biologics for JIA being etanercept, tocilizumab and adalimumab [122]. These drugs are available for multiple conditions and in 2015/16, NHS spending on these therapies approximated £550 million [438]. Several analyses have attempted to estimate the cost of improvement or quality-adjusted life year (QALY) associated with biologic therapies for CYP with JIA. In cohorts assessed between 2002 and 2008, the cost of an additional ACR-Pedi 30 response compared with MTX was estimated at between £8k and £24k depending on biologic choice [123] and £16k for both an additional QALY against MTX [439] and against placebo [440]. As the uptake of biosimilars increases for CYP with JIA [441], these costs may reduce by 20 to 40% [442] but even more important will be to reduce the non-response rate to therapies, reducing the cost per QALY further. Therefore, there remains a great financial incentive to further research towards an era of precision medicine.

Although the stratification of patients with JIA to different therapeutic strategies would be most beneficial at diagnosis, this thesis demonstrated few factors, measured at this time, which associated with later remission. If targeting remission using Wallace's preliminary criteria, it appears that older age may associate with higher achievement. However, many patient-reported outcomes associated with remission using the cJADAS10. This again corroborates the incorporation of patient-reported outcomes into clinical decision making. CYP with higher pain and poorer function and HRQoL could be targeted for early intervention by psychology, physiotherapy and/or occupational health. In addition, those from more socioeconomically deprived areas may be less likely to achieve remission according to the cJADAS10. These patients could additionally be targeted for these additional interventions.

Whilst specific predictors of different CID states may facilitate T2T strategies, there are barriers to implementing either CID according to Wallace's preliminary criteria or the cJADAS10 as treatment targets in clinic. The clinical implications of treating toward these specific targets may be the systematic under- or over-treating of patients depending on which definition of CID is targeted. High wellbeing as measured on the PGE could, in itself, capture any number of features with the greatest associations previously reported with pain and, to a lesser extent, function [160,213,353]. Targeting CID on Wallace's preliminary criteria in a CYP with high persistent pain or disability in the absence of inflammation may result in delayed or restricted access to relevant services such as psychology, physiotherapy and occupational health. Conversely, targeting CID on the JADAS in the same CYP with anti-rheumatic therapies may lead to unnecessarily pharmaceutical escalation to control symptoms not associated with inflammation. Thus, the nature of the therapeutic intervention(s) governs which treatment target may be optimal for use in a T2T strategy for use in clinical settings.

A second consideration for T2T strategies is whether to target CID in all CYP, or whether, in some cases, a target of MDA may be sufficient. For a selection of CYP, continuing to escalate interventions may not be in their best interests. This is reflected in T2T guidelines for RA, where low disease is targeted in patients where remission may not be a realistic aim [443]. This preliminary evidence in a cohort not treated according to any specific T2T strategy suggests that targeting CID may be beneficial if inflammation drives current poor disease status. However, CYP with CID had no greater function or HRQoL than those with MDA. Therefore, continuing to escalate therapies when these factors drive poor wellbeing may not be productive.

Feasibility of implementing these targets must also be considered. In terms of consistent capture of patients in CID or remission, the cJADAS10 is superior to Wallace's preliminary criteria. The requirement to have normal or zero scores on all criteria runs the risk of CYP not being classified in CID due to small variability around the zero end of the PGA whereas the cJADAS10 allows for this. The cJADAS10 also requires fewer components to be assessed and can be performed immediately with the patient, without the need to acquire additional information from ophthalmology or the laboratory.

Finally, the near 100% overlap in groups of CYP identified by the JADAS and cJADAS suggests that ESR does not need to be collected routinely in JIA clinical practice for the sole purpose of monitoring CID status. However, further work is needed to identify optimal targets for therapies using data where T2T strategies are consistently undertaken.

## 7.5 Future research

The work in this thesis has covered the quantification of remission in JIA globally, the comparison of achievement across definitions in a large inception cohort, the comparison of long-term outcomes following the achievement of these states and the assessment of factors associated with remission states. However, further research is needed in this area to be able to understand and target a clinically optimal definition of remission across JIA populations.

### 7.5.1 Future Qualitative Analyses: Understanding Remission

The main driver of discordance between current definitions of remission in JIA has been the inclusion or exclusion of patient-reported outcomes. The PGA and PGE have been previously demonstrated to correlate with different features of disease, PGA with inflammatory factors and PGE with pain and quality of life [160,195,418]. However, further qualitative work is needed to understand which factors are consistently being considered when physicians and families score across the full ranges of the PGA and PGE. Only then can we fully understand the construct of 'remission' being captured by current definitions to inform treatment strategies that may target these constructs. If different features of disease are considered within each scoring group, guidelines will need to be developed to standardise which features to consider when scoring the PGA and PGE. In addition, exact scoring of these measures requires standardisation. In a separate analysis to the creation of the CID cut-points using the JADAS, Consolaro et al. additionally developed JADAS cut-points for remission corresponding to a single subjective assessment of 'remission' versus 'no remission' by physicians, parents and children. All remission cut-points exceeded that

for CID [165,168]. Therefore, key features of disease activity are not weighted as highly by these groups as when developed against a more objective standard for CID.

Whilst understanding the drivers of individual outcome measures helps to discern which constructs they are capturing, further work is needed to understand the face and content validity of the full composite scores for remission in JIA, which have largely been overlooked for the published definitions. These analyses would involve qualitative work with families, patients and healthcare professionals to determine the acceptability of the composite outcome measures. If not acceptable to these groups, further changes may be needed to existing remission definitions.

### 7.5.2   Standardising Data Collection for JIA Research

The use of non-standardised remission criteria hinders both the evaluation of longer term outcomes and treatment effectiveness within JIA research studies. The use of non-comparable outcomes therefore slows down progress to build optimal treatment strategies for JIA and promotes the providing of less accurate information to patients and their families regarding the likely course of a CYP's disease. Standardised outcome measures are therefore a requirement. However, a limitation of adapting currently available remission criteria is the lack of easy available data for all component criteria. This could indicate the need for one or both of the following: a) the development of more clinically feasible remission criteria which are easier to capture in clinical practice and thus will be more complete in clinical research studies or b) the implementation of an international core item collection schedule. The latter is currently being developed in the UK [444] although the actual feasibility of such an approach is not known.

The strengths and limitations to developing more clinically feasible remission criteria have been previously discussed. However, if all component criteria were routinely collected, the development of new remission criteria may be unnecessary. At present, certain items are not clinically indicated for all patients e.g. the measurement of acute-phase reactants. In addition, certain items are intended for routine collection, but were incomplete in many patients in the CAPS cohort, e.g. PGA scores, pain measurements. If shown to be vital for treatment strategies, motivation for collecting such items may be impacted. However, if unfeasible, the guidelines on which measures are clinically indicated to collect would need revision. Therefore, the development of a clinically useful and feasible core item collection schedule for JIA may aid in the measuring and comparing of target state achievement within and across patient populations.

### 7.5.3 Novel Methods to Capture Data on Disease Activity in JIA

Alternative data sources to gain information regarding outcomes and predictors of outcomes in JIA include population health records and more novel electronic data capture methods. Large prospective inception cohorts such as CAPS are expensive and labour intensive. Therefore, looking for easier, cheaper and quicker ways to capture similar data to address these questions should be explored. Much of this burden is reduced when studying anonymised patient records, such as the Clinical Practice Research Datalink (CPRD) in the UK [445]. No formal consent is required and data from large populations, 7% of the UK population in CPRD [445], can be gained. However, datasets like CPRD are restricted to primary care settings and are limited in terms of which data they currently capture. Specifically, they do not currently capture disease specific measures for most conditions and do not even capture more generic outcomes such as a measure of function or HRQoL. Secondary care databases such as the England Hospital Episode Statistics (HES) database capture limited data on inpatients or day cases [446]. These are therefore a rich data source for certain outcomes in JIA, such as joint replacement surgeries, but like CPRD, do not capture more disease specific outcome measures. To capture alternative long-term outcomes such as vocational attainments, social factors and chronic pain, linkage to patient-reported data, which currently does not exist, would be needed. This could potentially be completed through novel data capture techniques, such as through the use of portable electronic devices. These devices may capture information automatically, such as step counts or sleep patterns [447] or may require active input from users [448]. Automatic data capture has the potential to monitor the impact of disease and may be captured on a daily basis with little missing data, provided the user keeps the electronic device on their person [447]. This would allow more granular data collection than the annual or bi-annual follow-ups in traditional observational JIA cohorts [297] and allow continuous follow-up following transfer to adult services. In addition, GPS data incorporated into many smart technologies would allow the assessment of certain environmental exposures, such as weather or pollutant levels [447]. These technologies often feature continuous wireless communication. Therefore, data collected could be automatically transferred into the electronic patient record [449] or to secure study centres [450,451], with the appropriate data governance and ethical approvals in place. The scope of data captured automatically through current means is limited in terms of medical outcomes, with patient-reported outcomes such as pain, fatigue and wellbeing not able to be fully captured. Incorporating patient-reported outcomes into electronic devices is, therefore, often vital [447,450]. However, this increases the likelihood of missing data through differing engagement patterns with

the electronic software [447,452]. This is particularly relevant given the long time-period needed to continuously capture changes in these outcomes, which may coincide with changes or updates to capture technologies. Engagement in the software or even the device holding the software may be prone to certain selection biases, with older generations less likely to own smart technology but more likely to engage with e-health applications for longer periods [447] but may be a preferred option for young people. However, for the youngest children with JIA, smart technologies are unlikely a feasible approach to capturing patient-reported outcomes. All options would not capture physician assessment of disease. Therefore, these technologies cannot currently be used to assess a full range of factors associated with, or outcomes following, remission in CYP with JIA.

### 7.5.4   Developing or Selecting a Target for T2T Strategies in JIA

Whilst this thesis cannot confirm an optimal target for T2T strategies in JIA or even if a T2T strategy would improve outcomes in JIA, the results have implications for their development. Firstly, more feasible targets do not necessarily result in greater misclassification in regards to the target state of interest. This was exemplified when comparing the JADAS and cJADAS, which differ only according to the inclusion or exclusion of ESR and identified almost 100% of the same CYP. In addition, the inclusion of greater than 10 joints did not change the group of CYP identified in CID compared with the 27 or 71 joint counts. This lesser requirement for data collection may aid in recruitment and analysis of research studies, where lesser burden in placed on patients who enrol, and on analysts for both trials and observational cohorts in terms of missing data.

For T2T strategies specifically, effectiveness has not yet been demonstrated in JIA. Therefore, the first step toward using these strategies would be a clinical trial of T2T versus current standard practice. Since Wallace's preliminary criteria captures an absence of inflammation, this may be a simpler initial target for the intervention arm of a trial focusing on anti-rheumatic therapies, such as MTX and biologics. The caveat would be that, if applied exactly and a facility to prevent end-point aversion is not explored, a group of CYP will likely be misclassified as not having achieved the outcome due to end-point aversion. To avoid the escalation of therapies in CYP clinically indistinguishable from those with no inflammation, the PGA score as part of Wallace's preliminary criteria should be set at a higher value than 0.0cm, for example 0.5cm.

A head-to-head trial may then be warranted with one arm targeting CID using Wallace's preliminary criteria and the other cJADAS10 to determine whether specifically targeting one definition of CID associates with a) faster achievement of CID and b) better outcomes.

This trial would, however, require the use of additional therapeutic options, such as physiotherapy, psychology and occupational health support, perhaps even with specific guidelines as to when to engage with these services. This would need to be adequately resourced as part of the trial. If needed, changes to resource allocation may then be necessary, such as greater funding for pain clinics. In addition, further trials would be needed on methods to discontinue medication whilst preventing disease flares after the states of CID have been achieved.

The discussed strategies, however, are only applicable to CYP with oligoarticular or polyarticular disease. Patients with the rarer ILAR categories, systemic, enthesitis-related, psoriatic and undifferentiated JIA, currently have few or no published criteria including the main features of their disease. Strategies additionally targeting the extra-articular features of these rarer categories would also, therefore, require trialling.

### 7.5.5 Extensions to Current Work using CAPS Data: Predictors of Remission

Few clinical factors at initial presentation to paediatric rheumatology associated with the achievement of CID within three years. Further work may therefore focus on genetic predictors in addition to 'omics data such as transcriptomic or proteomic data, which, as previously discussed, have rarely been investigated. Care will need to be taken to minimise the risk of 'the risk factor paradox' or 'collider stratification bias', whereby susceptibility factors appear to not associate with, or protect against, poor outcomes [453]. Such research should look beyond studying the effects of biomarkers already known to be associated with disease occurrence as there may be other biomarkers which influence disease severity after the disease has started, including factors which influence response to treatments. Further clinical factors may also prove predictive of CID than those identified in this thesis. Whilst a large cohort of CYP was able to be studied, the limited number of CYP achieving the outcomes of interest limited the number of factors that could be considered as predictors. CAPS continues to recruit and follow CYP. Thus, in time, additional predictors may be explored, such as psychosocial health and illness perception, inflammation in specific joints and biomarkers such as ANA and RF in addition to imaging results. Further research, potentially using other datasets, is needed to explore the impact of different therapeutic pathways, response to treatment as well as adherence to treatment.

Finally, the creation and validation of a robust prediction model for remission in JIA would allow the probability of remission for a given CYP to be gained in a clinical setting.

The model could be used to decide if more aggressive treatment strategies are warranted where low probabilities of achieving remission are evident. However, to be applicable in clinical practice, the model must have high predictive ability including explaining the majority of variance in remission achievement. It must also include items that are feasible to collect within a short appointment window and indicated in the majority of CYP, whilst recognising that what is feasible, particular in terms of biomarkers, may change. In addition, the probabilities must be easily calculable and may therefore involve the use of an online calculator or a tool built into clinical appointment interfaces.

# 8   FINAL CONCLUSIONS

In an era of biologic therapies, the burden of disease activity in JIA is high with the majority of CYP not achieving remission within the first three years of disease. Early aggressive treatment strategies may improve this burden, with greater improvements over the first year following diagnosis associated with achievement of remission. However, remission definitions for JIA currently identify different groups of CYP depending on whether an assessment of patient wellbeing is included. This thesis has demonstrated that wellbeing is key to long-term function and quality of life, with inflammation less associated with these outcomes. Both inflammation and wellbeing should therefore be incorporated into the monitoring of remission. Multiple therapeutic interventions would be needed to target this multifaceted disease state.

# 9 REFERENCES

(1) Petty RE, Southwood TR, Manners P, Baum J. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-392.

(2) Sakkas LI, Platsoucas CD. Immunopathogenesis of juvenile rheumatoid arthritis: role of T cells and MHC. Immunol Res 1995;14:218-236.

(3) Wynne-Roberts CR, Anderson CH, Turano AM, Baron M. Light- and electron-microscopic findings of juvenile rheumatoid arthritis synovium: comparison with normal juvenile synovium. Semin Arthritis Rheum 1978;7:287-302.

(4) Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME. Rheumatology, fourth edition. 2008.

(5) Guzman J, Oen K, Tucker LB, Huber AM, Shiff N, Boire G et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 2014.

(6) Oliveira-Ramos F, Eusebio M, Martins M, Mourao AF, Furtado C, Campanilho-Marques R et al. Juvenile idiopathic arthritis in adulthood: fulfilment of classification criteria for adult rheumatic diseases, long-term outcomes and predictors of inactive disease, functional status and damage. RMD Open 2016;2:e000304.

(7) Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford) 2002;41:1428-1435.

(8) Brewer EJ Jr., Bass J, Cassidy JT, Fink C, Jacobs J, Hanson V et al. Current Proposed Revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum 1977;20:195-199.

(9) Berntson L, Fasth A, Andersson-Gare B, Kristinsson J, Lahdenne P, Marhaug G et al. Construct validity of ILAR and EULAR criteria in juvenile idiopathic arthritis: a population based incidence study from the Nordic countries. International League of Associations for Rheumatology. European League Against Rheumatism. J Rheumatol 2001;28:2737-2743.

(10) Fink CW. Proposal for the Development of Classification Criteira for Idiopathic Arthritides of Childhood. The Journal of Rheumatology 1995;22:1566-1569.

(11) Bridges SL. Update on autoantibodies in rheumatoid arthritis. Curr Rheumatol Rep 2004;6:343-350.

(12) Ravelli A. Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. Clin Exp Rheumatol 2004;22:271-275.

(13) Belot A. New classification for juvenile idiopathic arthritis: Is the Tower of Babel falling? Joint Bone Spine 2018;85:139-141.

(14) Ravelli A, Varnier GC, Oliveira S, Castell E, Arguedas O, Magnani A et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:267-275.

(15) Ravelli A, Felici E, Magni-Manzoni S, Pistorio A, Novarini C, Bozzola E et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. Arthritis Rheum 2005;52:826-832.

(16) Prakken B, Albani S, Martini A. Juvenile Idiopathic Arthritis. The Lancet 2011;377:2138-2149.

(17)  Ombrello MJ, Arthur VL, Remmers EF, Hinks A, Tachmazidou I, Grom AA et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. Ann Rheum Dis 2017;76:906-913.

(18)  Angeles-Han ST, Pelajo CF, Vogler LB, Rouster-Stevens K, Kennedy C, Ponder L et al. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol 2013;40:2088-2096.

(19)  Moradi A, Amin RM, Thorne JE. The role of gender in juvenile idiopathic arthritis-associated uveitis. J Ophthalmol 2014;2014:461078.

(20)  Yu HH, Chen PC, Wang LC, Lee JH, Lin YT, Yang YH et al. Juvenile idiopathic arthritis-associated uveitis: a nationwide population-based study in Taiwan. PLos One 2013;8:e70625-doi:10.1371/journal.pone.0070625.

(21)  Heiligenhaus A, Heinz C, Edelsten C, Kotaniemi K, Minden K. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. Ocul Immunol Inflamm 2013;21:180-191.

(22)  Clarke SLN, Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Pediatric Rheumatology 2016;14.

(23)  British Society for Paediatric and Adolescent Rheumatology, Royal College of Ophthalmology. Guidelines for screening for Uveitis in Juvenile idiopathic arthritis. 2006.

(24)  Davies K, Cleary G, Foster H, Hutchinson E, Baildam E. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford) 2010;49:1406-1408.

(25)  Prieur AM, Le Gall E FAU - Karman, Karman FF, Edan CF, Lasserre OF, Goujard J. Epidemiologic survey of juvenile chronic arthritis in France. Comparison of data obtained from two different regions. Clin Exp Rheumatol 1987;5.

(26)  Savolainen E, Kaipiainen-Seppanen O, Kroger L, Luosujarvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 arthritis survey. J Rheumatol 2003;30:2460-2468.

(27)  Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014;81:112-117.

(28)  Huang JL, Yao TC, See LC. Prevalence of pediatric systemic lupus erythematosus and juvenile chronic arthritis in a Chinese population: a nation-wide prospective population-based study in Taiwan. Clin Exp Rheumatol 2004;22:776-780.

(29)  Manners PJ, Diepeveen DA. Prevalence of juvenile chronic arthritis in a population of 12-year-old children in urban Australia. Pediatrics 1996;98:84-90.

(30)  Shen CC, Yeh KW, Ou LS, Yao TC, Chen LC, Huang JL. Clinical features of children with juvenile idiopathic arthritis using the ILAR classification criteria: a community-based cohort study in Taiwan. J Microbiol Immunol Infect 2013;46:288-294.

(31)  Cassidy JT, Petty RE. Textbook of pediatric rheumatology. Elsevier Saunders, 2005.

(32)  Ogilvie EM, Fife MS, Thompson SD, Twine N, Tsoras M, Moroldo M et al. The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families. Arthritis Rheum 2003;48:3202-3206.

(33)  Prahalad S, Glass DN. A comprehensive review of the genetics of juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2008;6:11.

(34) Shenoi S, Shaffer ML, Wallace CA. Environmental Risk Factors and Early-Life Exposures in Juvenile Idiopathic Arthritis: A Case-Control Study. Arthritis Care Res (Hoboken ) 2016;68:1186-1194.

(35) Carlens C, Jacobsson L, Brandt L, Cnattingius S, Stephansson O, Askling J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. Ann Rheum Dis 2009;68:1159-1164.

(36) Ellis JA, Ponsonby AL, Pezic A, Chavez RA, Allen RC, Akikusa JD et al. CLARITY - ChiLdhood Arthritis Risk factor Identification sTudY. Pediatr Rheumatol Online J 2012;10:37.

(37) Shenoi S, Bell S, Wallace CA, Mueller BA. Juvenile idiopathic arthritis in relation to maternal prenatal smoking. Arthritis Care Res (Hoboken ) 2015;67:725-730.

(38) Jaakkola JJK, Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. Int J Epidemiol 2005;34:664-671.

(39) Zeft AS, Prahalad S, Lefevre S, Clifford B, McNally B, Bohnsack JF et al. Juvenile idiopathic arthritis and exposure to fine particulate air pollution. Clin Exp Rheumatol 2009;27:877-884.

(40) Zeft AS, Prahalad S, Schneider R, Dedeoglu F, Weiss PF, Grom AA et al. Systemic onset juvenile idiopathic arthritis and exposure to fine particulate air pollution. Clin Exp Rheumatol 2016;34:946-952.

(41) Phillips DH, Hewer A, Martin CN, Garner RC, King MM. Correlation of DNA adduct levels in human lung with cigarette smoking. Nature 1988;336:790-792.

(42) Phillips DH, Venitt S. DNA and protein adducts in human tissues resulting from exposure to tobacco smoke. Int J Cancer 2012;131:2733-2753.

(43) IARC. IARC monographs on the evaluation of carcinogenic risks to humans. A review of human carcinogens: personal habits and indoor combustions. 2012.

(44) Chang K, Yang SM, Kim SH, Han KH, Park SJ, Shin JI. Smoking and Rheumatoid Arthritis. International Journal of Molecular Sciences 2014;15:22279-22295.

(45) Phillips DH. Biomarkers of human exposure to environmental tobacco smoke (ETS). In: Knudsen LE, Merlo DF, editors. Biomarkers and human biomonitoring. Cambridge: Royal Society of Chemistry, 2012:23-49.

(46) Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70-81.

(47) Neu J, Rushing J. Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol 2011;38:321-331.

(48) Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy 2008;38:629-633.

(49) Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia 2008;51:726-735.

(50) Sevelsted A, Stokholm J, Bonnelykke K, Bisgaard H. Cesarean section and chronic immune disorders. Pediatrics 2015;135:e92-e98.

(51) Lavender T, Hofmeyr GJ, Neilson JP, Kingdon C, Gyte GM. Caesarean section for non-medical reasons at term. Cochrane Database Syst Rev 2006;CD004660.

(52)  Hanson LA. Breastfeeding provides passive and likely long-lasting active immunity. Ann Allergy Asthma Immunol 1998;81:523-533.

(53)  Rosenberg AM. Evaluation of associations between breast feeding and subsequent development of juvenile rheumatoid arthritis. J Rheumatol 1996;23:1080-1082.

(54)  Kindgren E, Fredrikson M, Ludvigsson J. Early feeding and risk of Juvenile idiopathic arthritis: a case control study in a prospective birth cohort. Pediatr Rheumatol Online J 2017;15:46.

(55)  Mason T, Rabinovich CE, Fredrickson DD, Amoroso K, Reed AM, Stein LD et al. Breast feeding and the development of juvenile rheumatoid arthritis. J Rheumatol 1995;22:1166-1170.

(56)  Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55 Suppl 1:S2-10.

(57)  Miller J, Ponsonby AL, Pezic A, Kemp A, Piper SE, Akikusa JD et al. Sibling Exposure and Risk of Juvenile Idiopathic Arthritis. Arthritis Rheumatol 2015;67:1951-1958.

(58)  Nielsen HE, Dorup J, Herlin T, Larsen K, Nielsen S, Pedersen FK. Epidemiology of juvenile chronic arthritis: risk dependent on sibship, parental income, and housing. J Rheumatol 1999;26:1600-1605.

(59)  Prahalad S, Fraser AM, O'Brien E, Kerber RA, Mineau GP, Bohnsack JF. Lack of association between birth order and juvenile idiopathic arthritis. Arthritis Rheum 2003;48:2989-2990.

(60)  Ellis JA, Munro JE, Ponsonby AL. Possible environmental determinants of juvenile idiopathic arthritis. Rheumatology (Oxford) 2010;49:411-425.

(61)  Lindsley CB. Seasonal variation in systemic onset juvenile rheumatoid arthritis. Arthritis Rheum 1987;30:838-839.

(62)  Oen K, Fast MF, Postl B. Epidemiology of juvenile rheumatoid arthritis in Manitoba, Canada, 1975-92: cycles in incidence. J Rheumatol 1995;22.

(63)  Nielsen PR, Kragstrup TW, Deleuran BW, Benros ME. Infections as risk factor for autoimmune diseases - A nationwide study. J Autoimmun 2016;74:176-181.

(64)  Angelini F, Cancrini C, Colavita M, Panei P, Concato C, Romiti ML et al. Role of parvovirus B19 infection in juvenile chronic arthritis. Is more investigation needed? Clin Exp Rheumatol 2003;21:684.

(65)  Bosma TJ, Etherington J, O'Shea S, Corbett K, Cottam F, Holt L et al. Rubella virus and chronic joint disease: is there an association? J Clin Microbiol 1998;36:3524-3526.

(66)  Pritchard MH, Matthews N, Munro J. Antibodies to influenza A in a cluster of children with juvenile chronic arthritis. Br J Rheumatol 1988;27:176-180.

(67)  Weissbrich B, Suss-Frohlich Y, Girschick HJ. Seroprevalence of parvovirus B19 IgG in children affected by juvenile idiopathic arthritis. Arthritis Res Ther 2007;9:R82.

(68)  Arvonen M, Virta LJ, Pokka T, Kroger L, Vahasalo P. Repeated exposure to antibiotics in infancy: a predisposing factor for juvenile idiopathic arthritis or a sign of this group's greater susceptibility to infections? J Rheumatol 2015;42:521-526.

(69)  Horton DB, Scott FI, Haynes K, Putt ME, Rose CD, Lewis JD et al. Antibiotic Exposure and Juvenile Idiopathic Arthritis: A Case-Control Study. Pediatrics 2015;136:e333-e343.

(70)  Arvonen M, Berntson L, Pokka T, Karttunen TJ, Vahasalo P, Stoll ML. Gut microbiota-host interactions and juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2016;14:44.

(71)  Mathew JL, Singh S, Sankar J. Is antibiotic exposure associated with newly diagnosed juvenile idiopathic arthritis? Indian Pediatr 2015;52:883-888.

(72) Smith T, Noble M, Noble S, Wright G, McLennan D, Plunkett E. The English Indices of Deprivation 2015. Department for Communities and Local Government 2015.

(73) Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. Am J Public Health 1992;82:816-820.

(74) Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. Ann N Y Acad Sci 1999;896:3-15.

(75) Pampel FC, Krueger PM, Denney JT. Socioeconomic Disparities in Health Behaviors. Annual Review of Sociology 2010;36:349-370.

(76) Oakley LL, Renfrew MJ, Kurinczuk JJ, Quigley MA. Factors associated with breastfeeding in England: an analysis by primary care trust. BMJ Open 2013;3.

(77) Flacking R, Nyqvist KH, Ewald U. Effects of socioeconomic status on breastfeeding duration in mothers of preterm and term infants. Eur J Public Health 2007;17:579-584.

(78) Van Roode T, Sharples K, Dickinson N, Paul C. Life-Course Relationship between Socioeconomic Circumstances and Timing of First Birth in a Birth Cohort. PLos One 2017;12:e0170170.

(79) Huber S, Bookstein FL, Fieder M. Socioeconomic status, education, and reproduction in modern women: an evolutionary perspective. Am J Hum Biol 2010;22:578-587.

(80) Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum 2007;56:1974-1984.

(81) Kurahara D, Tokuda A, Grandinetti A, Najita J, Ho C, Yamamoto K et al. Ethnic differences in risk for pediatric rheumatic illness in a culturally diverse population. J Rheumatol 2002;29:379-383.

(82) Fujikawa S, Okuni M. A nationwide surveillance study of rheumatic diseases among Japanese children. Acta Paediatr Jpn 1997;39:242-244.

(83) Khuffash FA, Majeed HA, Lubani MM, Najdi KN, Gunawardana SS, Bushnaq R. Epidemiology of juvenile chronic arthritis and other connective tissue diseases among children in Kuwait. Ann Trop Paediatr 1990;10:255-259.

(84) Abdwani R, Abdella E, Abrawi S, Al-Zakwani I. Epidemiology of juvenile idiopathic arthritis in Oman. Pediatric Rheumatology Online Journal 2015;13:33.

(85) Usenbo A, Kramer V, Young T, Musekiwa A. Prevalence of Arthritis in Africa: A Systematic Review and Meta-Analysis. PLos One 2015;10:e0133858.

(86) Sawhney S. Tertiary level paediatric rheumatology in India. Pediatr Rheumatol Online J 2003;1:184.

(87) Hussain-Gambles M. Ethnic minority under-representation in clinical trials. Whose responsibility is it anyway? J Health Organ Manag 2003;17:138-143.

(88) Mason S, Hussain-Gambles M, Leese B, Atkin K, Brown J. Representation of South Asian people in randomised clinical trials: analysis of trials' data. BMJ 2003;326:1244-1245.

(89) Hussain-Gambles M, Atkin K, Leese B. Why ethnic minority groups are under-represented in clinical trials: a review of the literature. Health Soc Care Community 2004;12:382-388.

(90) Hussain-Gambles M, Atkin K, Leese B. South Asian participation in clinical trials: the views of lay people and health professionals. Health Policy 2006;77:149-165.

(91) Hussain-Gambles M. South Asian patients' views and experiences of clinical trial participation. Fam Pract 2004;21:636-642.

(92) Marshall SL, While AE. Interviewing respondents who have English as a second language: challenges encountered and suggestions for other researchers. J Adv Nurs 1994;19:566-571.

(93) Newman PA, Duan N, Roberts KJ, Seiden D, Rudy ET, Swendeman D et al. HIV vaccine trial participation among ethnic minority communities: barriers, motivators, and implications for recruitment. J Acquir Immune Defic Syndr 2006;41:210-217.

(94) Arean PA, Alvidrez J, Nery R, Estes C, Linkins K. Recruitment and retention of older minorities in mental health services research. Gerontologist 2003;43:36-44.

(95) Hinton L, Guo Z, Hillygus J, Levkoff S. Working with culture: a qualitative analysis of barriers to the recruitment of Chinese-American family caregivers for dementia research. J Cross Cult Gerontol 2000;15:119-137.

(96) Elkan R, Avis M, Cox K, Wilson E, Patel S, Miller S et al. The reported views and experiences of cancer service users from minority ethnic groups: a critical review of the literature. Eur J Cancer Care (Engl ) 2007;16:109-121.

(97) Hodge FS, Weinmann S, Roubideaux Y. Recruitment of American Indians and Alaska Natives into clinical trials. Ann Epidemiol 2000;10:S41-S48.

(98) Chang BH, Hendricks AM, Slawsky MT, Locastro JS. Patient recruitment to a randomized clinical trial of behavioral therapy for chronic heart failure. BMC Med Res Methodol 2004;4:8.

(99) Petrovitch H, Byington R, Bailey G, Borhani P, Carmody S, Goodwin L et al. Systolic Hypertension in the Elderly Program (SHEP). Part 2: Screening and recruitment. Hypertension 1991;17:II16-II23.

(100) Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999;52:1143-1156.

(101) Lovato LC, Hill K, Hertert S, Hunninghake DB, Probstfield JL. Recruitment for controlled clinical trials: literature summary and annotated bibliography. Control Clin Trials 1997;18:328-352.

(102) Stone VE, Mauch MY, Steger KA. Provider attitudes regarding participation of women and persons of color in AIDS clinical trials. Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology 1998;19:245-253.

(103) Thompson EE, Neighbors HW, Munday C, Jackson JS. Recruitment and retention of African American patients for clinical research: an exploration of response rates in an urban psychiatric hospital. J Consult Clin Psychol 1996;64:861-867.

(104) van RM, Burke J. The effect of patient race and socio-economic status on physicians' perceptions of patients. Soc Sci Med 2000;50:813-828.

(105) Swanson GM, Ward AJ. Recruiting minorities into clinical trials: toward a participant-friendly system. J Natl Cancer Inst 1995;87:1747-1759.

(106) Kahn PJ. Juvenile idiopathic arthritis - what the clinician needs to know. Bull Hosp Jt Dis (2013) 2013;71:194-199.

(107) Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) 2011;63:465-482.

(108) NHS England Clinical Reference Group for Paediatric Medicine. Interim Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA).  2015.

(109) Katsicas MM, Ricardo A, Russo G. Corticosteroids in Juvenile Idiopathic Arthritis. Systemic Corticosteroids for Inflammatory Disorders in Pediatrics. Springer International Publishing, 2015:59-76.

(110) Padeh S, Passwell JH. Intraarticular corticosteroid injection in the management of children with chronic arthritis. Arthritis Rheum 1998;41:1210-1214.

(111) Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. Arch Dis Child 2003;88:197-200.

(112) Ravelli A, Viola S, Ramenghi B, Beluffi G, Zonta LA, Martini A. Radiologic progression in patients with juvenile chronic arthritis treated with methotrexate. J Pediatr 1998;133:262-265.

(113) Graham LD, Myones BL, Rivas-Chacon RF, Pachman LM. Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. J Pediatr 1992;120:468-473.

(114) Falvey S, Shipman L, Ilowite N, Beukelman T. Methotrexate-induced nausea in the treatment of juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2017;15:52.

(115) Klein A, Kaul I, Foeldvari I, Ganser G, Urban A, Horneff G. Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: an observational study with patients from the German Methotrexate Registry. Arthritis Care Res (Hoboken ) 2012;64:1349-1356.

(116) Murray KJ, Lovell DJ. Advanced therapy for juvenile arthritis. [Review] [86 refs]. Best Practice & Research in Clinical Rheumatology 2002;16:361-78.

(117) Mulligan K, Kassoumeri L, Etheridge A, Moncrieffe H, Wedderburn LR, Newman S. Mothers' reports of the difficulties that their children experience in taking methotrexate for Juvenile Idiopathic Arthritis and how these impact on quality of life. Pediatr Rheumatol Online J 2013;11:23.

(118) National Institute for Health and Care Excellence. Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. 2002.

(119) European Medicines Agency. EPAR summary for the public: Enbrel. 2014.

(120) European Medicines Agency. European public assessment reports: Arthritis, Juvenile Rheumatoid. 2017.

(121) European Medicines Agency. Opinions and decisions on paediatric investigation plans. 2017.

(122) Kearsley-Fleet L, Davies R, Baildam E, Beresford MW, Foster HE, Southwood TR et al. Factors associated with choice of biologic among children with Juvenile Idiopathic Arthritis: results from two UK paediatric biologic registers. Rheumatology (Oxford) 2016;55:1556-1565.

(123) Ungar WJ, Costa V, Hancock-Howard R, Feldman BM, Laxer RM. Cost-effectiveness of biologics in polyarticular-course juvenile idiopathic arthritis patients unresponsive to disease-modifying antirheumatic drugs. Arthritis Care Res (Hoboken) 2011;63:111-119.

(124) Davies R, Carrasco R, Foster HE, Baildam EM, Chieng SE, Davidson JE et al. Treatment prescribing patterns in patients with juvenile idiopathic arthritis (JIA): Analysis from the UK Childhood Arthritis Prospective Study (CAPS). Semin Arthritis Rheum 2016;46:190-195.

(125) Stinson JN, Luca NJ, Jibb LA. Assessment and management of pain in juvenile idiopathic arthritis. Pain Res Manag 2012;17:391-396.

(126) Kvien TK, Hoyeraal HM, Sandstad B. Naproxen and acetylsalicylic acid in the treatment of pauciarticular and polyarticular juvenile rheumatoid arthritis. Assessment of tolerance and efficacy in a single-centre 24-week double-blind parallel study. Scand J Rheumatol 1984;13:342-350.

(127) Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, Ravelli A, Loy A, Murray KJ et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. Ann Rheum Dis 2008;67:309-314.

(128) Prince FH, Geerdink LM, Borsboom GJ, Twilt M, Van Rossum MA, Hoppenreijs EP et al. Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis. Ann Rheum Dis 2010;69:138-142.

(129) Ruperto N, Lovell DJ, Li T, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken ) 2010;62:1542-1551.

(130) Kimura Y, Walco GA. Treatment of chronic pain in pediatric rheumatic disease. Nat Clin Pract Rheumatol 2007;3:210-218.

(131) Lovell DJ, Walco GA. pain associated with juvenile rheumatoid arthritis. Pediatric Clinics of North America 1989;36:1015-1027.

(132) Sherry DD, Bohnsack J, Salmonson K, Wallace CA, Mellins E. Painless juvenile rheumatoid arthritis. J Pediatr 1990;116:921-923.

(133) Connelly M, Schanberg L. Opioid therapy for the treatment of refractory pain in children with juvenile rheumatoid arthritis. Nat Clin Pract Rheumatol 2006;2:636-637.

(134) Kimura Y, Walco GA, Sugarman E, Conte PM, Schanberg LE. Treatment of pain in juvenile idiopathic arthritis: a survey of pediatric rheumatologists. Arthritis Rheum 2006;55:81-85.

(135) Sawyer MG, Whitham JN, Roberton DM, Taplin JE, Varni JW, Baghurst PA. The relationship between health-related quality of life, pain and coping strategies in juvenile idiopathic arthritis. Rheumatology (Oxford) 2004;43:325-330.

(136) Shaw KL, Southwood TR, Duffy CM, McDonagh JE. Health-related quality of life in adolescents with juvenile idiopathic arthritis. Arthritis Rheum 2006;55:199-207.

(137) Butbul AY, Stremler R, Benseler SM, Cameron B, Laxer RM, Ota S et al. Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. Rheumatology (Oxford) 2011;50:2051-2060.

(138) Takken T, Van Der Net J, Helders PJ. Relationship between functional ability and physical fitness in juvenile idiopathic arthritis patients. Scand J Rheumatol 2003;32:174-178.

(139) Takken T, Hemel A, Van Der Net J, Helders PJ. Aerobic fitness in children with juvenile idiopathic arthritis: a systematic review. J Rheumatol 2002;29:2643-2647.

(140) Hackett J, Johnson B, Parkin A, Southwood T. Paediatric rheumatology: clinical practice review. Physiotherapy and occupational therapy for juvenile chronic arthritis: custom and practice in five centres in the UK, USA and Canada. Br J Rheumatol 1996;35:695-699.

(141) Klepper SE. Effects of an eight-week physical conditioning program on disease signs and symptoms in children with chronic arthritis. Arthritis Care Res 1999;12:52-60.

(142) Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M et al. Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis. Health Technol Assess 2005;9:iii-x, 1.

(143) Singh-Grewal D, Wright V, Bar-Or O, Feldman BM. Pilot study of fitness training and exercise testing in polyarticular childhood arthritis. Arthritis Rheum 2006;55:364-372.

(144) Stinson J, Wilson R, Gill N, Yamada J, Holt J. A systematic review of internet-based self-management interventions for youth with health conditions. J Pediatr Psychol 2009;34:495-510.

(145) Stinson JN, McGrath PJ, Hodnett ED, Feldman BM, Duffy CM, Huber AM et al. An internet-based self-management program with telephone support for adolescents with arthritis: a pilot randomized controlled trial. J Rheumatol 2010;37:1944-1952.

(146) Jensen MP. A neuropsychological model of pain: research and clinical implications. J Pain 2010;11:2-12.

(147) Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. Pain 2010;148:387-397.

(148) Walco GA, Varni JW, Ilowite NT. Cognitive-behavioral pain management in children with juvenile rheumatoid arthritis. Pediatrics 1992;89:1075-1079.

(149) Lavigne JV, Ross CK, Berry SL, Hayford JR, Pachman LM. Evaluation of a psychological treatment package for treating pain in juvenile rheumatoid arthritis. Arthritis Care Res 1992;5:101-110.

(150) Abdel MP, Figgie MP. Surgical management of the juvenile idiopathic arthritis patient with multiple joint involvement. Orthop Clin North Am 2014;45:435-442.

(151) Bou R, Adan A, Borras F, Bravo B, Calvo I, De IJ et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int 2015;35:777-785.

(152) Smitherman EA, Consolaro A, Morgan EM. Treat to Target in Juvenile Idiopathic Arthritis: Challenges and Opportunities. Current Treatment Opinions in Rheumatology 2018;[online first].

(153) Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3-15.

(154) Schoels M, Knevel R, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas DT et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis 2010;69:638-643.

(155) Wallace CA. Developing standards of care for patients with juvenile idiopathic arthritis. Rheumatology (Oxford) 2010;49:1213-1214.

(156) Consolaro A, Negro G, Lanni S, Solari N, Martini A, Ravelli A. Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. Clin Exp Rheumatol 2012;30:S157-S162.

(157) McErlane F, Beresford MW, Baildam EM, Thomson W, Hyrich KL. Recent developments in disease activity indices and outcome measures for juvenile idiopathic arthritis. Rheumatology (Oxford) 2013;52:1941-1951.

(158) Consolaro A, Calandra S, Robbiano C, Ravelli A. Treating Juvenile Idiopathic Arthritis According to JADAS-Based Targets. Ann Paediatr Rheum 2014;3:4-10.

(159) Vuorimaa H, Tamm K, Honkanen V, Konttinen YT, Komulainen E, Santavirta N. Empirical classification of children with JIA: a multidimensional approach to pain and well-being. Clin Exp Rheumatol 2008;26:954-961.

(160) Sztajnbok F, Coronel-Martinez DL, Diaz-Maldonado A, Novarini C, Pistorio A, Viola S et al. Discordance between physician's and parent's global assessments in juvenile idiopathic arthritis. Rheumatology (Oxford) 2007;46:141-145.

(161) Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-1209.

(162)   Delbecq AL, Van de Ven AH, Gustafson DH. Group Techniques for Program Planning: A Guide to Nominal Groups and Delphi Process. Scott Foresman Company Glenview, 1975.

(163)   Keeley T, Williamson P, Callery P, Jones LL, Mathers J, Jones J et al. The use of qualitative methods to inform Delphi surveys in core outcome set development. Trials 2016;17:230.

(164)   Macefield RC, Boulind CE, Blazeby JM. Selecting and measuring optimal outcomes for randomised controlled trials in surgery. Langenbecks Arch Surg 2014;399:263-272.

(165)   Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290-2294.

(166)   Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305-310.

(167)   National Institute for Health and Clinical Excellence. The guidelines manual.  2009.

(168)   Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. Arthritis Rheum 2012;64:2366-2374.

(169)   Tammela O. Applications of consensus methods in the improvement of care of paediatric patients: a step forward from a 'good guess'. Acta Paediatrica 102, 111-115. 2012.

(170)   Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLos One 2011;6:e20476.

(171)   Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-753.

(172)   Goodman CM. The Delphi technique: a critique. J Adv Nurs 1987;12:729-734.

(173)   Scheibe M, Skutsch M, Schofer J. Experiments in Delphi Methodology. In: Linestone H, Turoff M, editors. The Delphi Method: Techniques and Applications . Addison-Wesley, 1975.

(174)   Brunner HI, Ravelli A. Developing outcome measures for paediatric rheumatic diseases. Best Pract Res Clin Rheumatol 2009;23:609-624.

(175)   Baird C, Wagner D. The relative validity of actuarial- and consensus-based risk assessment systems. Children and Youth Services Review 22[11-12], 839-871. 2000.

(176)   Regnault A, Gilet H, Meunier J, Arnould B. Statistical approach to development and validation of patient-reported outcomes tools for individual decision-making.  2011.

(177)   Gargon E, Williamson PR, Altman DG, Blazeby JM, Clarke M. The COMET Initiative database: progress and activities from 2011 to 2013. Trials 2014;15:279.

(178)   Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 2010;19:539-549.

(179)   Patient-Centred Outcomes Research Institute. Preliminary Draft Methodology Report: "Our Questions, Our Decisions: Standards for Patient-centred Outcomes Research". Helfand M, Berg A, Flum D, Gabriel S, editors.  2012.

(180)   Boers M, Kirwan JR, Tugwell P, Beaton D, Bingham CO, III, Conaghan PG et al. The OMERACT Handbook. 2017.

(181) Wallace CA, Ravelli A, Huang B, Giannini EH. Preliminary validation of clinical remission criteria using the OMERACT filter for select categories of juvenile idiopathic arthritis. J Rheumatol 2006;33:789-795.

(182) Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J 2012;24:69-71.

(183) Lalkhen AG, McCluskey A. Clinical tests: sensitivity and specificity. Continuing Education in Anaesthesia Critical Care & Pain 8[6], 221-223. 2008.

(184) Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016;15:155-163.

(185) Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929-936.

(186) Consolaro A, Negro G, Gallo MC, Bracciolini G, Ferrari C, Schiappapietra B et al. Defining criteria for disease activity states in non-systemic juvenile idiopathic arthritis based on a three-variable Juvenile Arthritis Disease Activity Score. Arthritis Care Res (Hoboken) 2014;66:1703-9.

(187) Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum 2008;59:1120-1127.

(188) Nugent J, Grainer J, Machado C. The British version of the childhood health assessment questionnaire (CHAQ) and the child health questionnaire (CHQ). Clin Exp Rheumatol 2001;19:S163-7.

(189) Cassidy JT, Levinson JE, Bass JC, Baum J, Brewer EJ, Jr., Fink CW et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum 1986;29:274-281.

(190) Magni-Manzoni S, Cugno C, Pistorio A, Garay S, Tsitsami E, Gasparini C et al. Responsiveness of clinical measures to flare of disease activity in juvenile idiopathic arthritis. Clin Exp Rheumatol 2005;23:421-425.

(191) Klepper SE, Scull SA. Juvenile Rheumatoid Arthritis. 1999:429-468.

(192) Muller L, Kellenberger CJ, Cannizzaro E, Ettlin D, Schraner T, Bolt IB et al. Early diagnosis of temporomandibular joint involvement in juvenile idiopathic arthritis: a pilot study comparing clinical examination and ultrasound to magnetic resonance imaging. Rheumatology (Oxford) 2009;48:680-685.

(193) Recommendation of measurement of erythrocyte sedimentation rate of human blood. Am J Clin Pathol 1977;68:505-507.

(194) Piva E, Sanzari MC, Servidio G, Plebani M. Length of sedimentation reaction in undiluted blood (erythrocyte sedimentation rate): variations with sex and age and reference limits. Clin Chem Lab Med 2001;39:451-454.

(195) Palmisani E, Solari N, Magni-Manzoni S, Pistorio A, Labo E, Panigada S et al. Correlation between juvenile idiopathic arthritis activity and damage measures in early, advanced, and longstanding disease. Arthritis Care and Research 2006;55:843-849.

(196) Sarkar S, Alam MM, Das G, Datta S. Inflammatory Markers and Disease Activity in Juvenile Idiopathic Arthritis. Indian J Pediatr 2017;84:349-356.

(197) Harrison M. Erythrocyte sedimentation rate and C-reactive protein. Aust Prescr 2015;38:93-94.

(198)  McErlane F, Beresford MW, Baildam EM, Chieng SEA, Davidson JE, Foster HE et al. Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. Ann Rheum Dis 2013;72:1983-1988.

(199)  Miller ML, Ruprecht J, Wang D, Zhou Y, Lales G, McKenna S et al. Physician assessment of disease activity in JIA subtypes. Analysis of data extracted from electronic medical records. Pediatr Rheumatol Online J 2011;9:9.

(200)  Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37:1761-9.

(201)  Taylor J, Giannini EH, Lovell DJ, Huang B, Morgan EM. Lack of Concordance in Interrater Scoring of the Provider's Global Assessment of Children With Juvenile Idiopathic Arthritis With Low Disease Activity. Arthritis Care Res (Hoboken ) 2018;70:162-166.

(202)  Turk M, Pope JE. Physician global assessment for disease activity in rheumatoid arthritis are all over the map! RMD Open 2018;4.

(203)  Lal SD, McDonagh J, Baildam E, Wedderburn LR, Gardner-Medwin J, Foster HE et al. Agreement between proxy and adolescent assessment of disability, pain, and well-being in juvenile idiopathic arthritis. J Pediatr 2011;158:307-312.

(204)  van Mater HA, Williams JW, Jr., Coeytaux RR, Sanders GD, Kemper AR. Psychometric characteristics of outcome measures in juvenile idiopathic arthritis: a systematic review. Arthritis Care Res (Hoboken) 2012;64:554-562.

(205)  Filocamo G, Sztajnbok F, Cespedes-Cruz A, Magni-Manzoni S, Pistorio A, Viola S et al. Development and validation of a new short and simple measure of physical function for juvenile idiopathic arthritis. Arthritis Rheum 2007;57:913-920.

(206)  Iglesias MJ, Cuttica RJ, Herrera Calvo M, Micelotta M, ringe A, rusco MI. Design and validation of a new scale to assess the functional ability in children with juvenile idiopathic arthritis (JIA). Clin Exp Rheumatol 2006;24:713-8.

(207)  Palermo TM, Witherspoon DF, Valenzuela DF, Drotar DD. Development and validation of the Child Activity Limitations Interview: a measure of pain-related functional impairment in school-age children and adolescents. Pain 2004;109:461-70.

(208)  Daltroy LH, Liang MH, Fossel AH, Goldberg MJ. The POSNA pediatric musculoskeletal functional health questionnaire: report on reliability, validity, and sensitivity to change. Pediatric Outcomes Instrument Development Group. Pediatric Orthopaedic Society of North America. J Pediatr Orthop 1998;18:561-71.

(209)  Feldman AB, Haley SM., Coryell J. Concurrent and construct validity of the Pediatric Evaluation of Disability Inventory. Phys Ther 1990;70:602-10.

(210)  Wright FV, Law M, Crombie V, Goldsmith CH, Dent P. Development of a self-report functional status index for juvenile rheumatoid arthritis. J Rheumatol 1994;21:536-44.

(211)  Kirwan JR, Reeback JS. Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis. Br J Rheumatol 1986;25:206-209.

(212)  Dempster H, Porepa M, Young N, Feldman BM. The clinical meaning of functional outcome scores in children with juvenile arthritis. Arthritis Rheum 2001;44:1768-1774.

(213)  Palmisani E, Solari N, Magni-Manzoni S, Pistorio A, Labo E, Panigada S et al. Correlation between juvenile idiopathic arthritis activity and damage measures in early, advanced, and longstanding disease. Arthritis Rheum 2006;55:843-849.

(214)  Luca NJC, Feldman BM. Health outcomes of pediatric rheumatic diseases. Best Pract Res Clin Rheumatol 2014;28:331-350.

(215) Boiu S, Marniga E, Bader-Meunier B, Mouy R, Compeyrot-Lacassagne S, Quartier P et al. Functional status in severe juvenile idiopathic arthritis in the biologic treatment era: an assessment in a French paediatric rheumatology referral centre. Rheumatology (Oxford) 2012;51:1285-1292.

(216) McHorney CA. Generic health measurement: past accomplishments and a measurement paradigm for the 21st century. Ann Intern Med 1997;127:743-750.

(217) Klepper SE. Measures of pediatric function: Child Health Assessment Questionnaire (C-HAQ), Juvenile Arthritis Functional Assessment Scale (JAFAS), Pediatric Outcomes Data Collection Instrument (PODCI), and Activities Scale for Kids (ASK). Arthritis Care Res (Hoboken ) 2011;63 Suppl 11:S371-S382.

(218) de JW, Hoppenreijs EP, Wulffraat NM, Wedderburn LR, Kuis W, Prakken BJ. Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. Ann Rheum Dis 2007;66:589-598.

(219) Balan S. Approach to Joint Pain in Children. Indian J Pediatr 2016;83:135-139.

(220) Allegra M, Gallo MC, Verazza S, Calandra S, Dalpra S, Mongelli F et al. Is it worth allowing the presence of morning stiffness in the definition of inactive disease in juvenile idiopathic arthritis? Pediatr Rheumatol Online J 2014;12:174.

(221) Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis 2004;63:1638-1644.

(222) Kietz DA, Pepmueller PH, Moore TL. Clinical response to etanercept in polyarticular course juvenile rheumatoid arthritis. J Rheumatol 2001;28:360-362.

(223) Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two year period. Ann Rheum Dis 2002;61:171-173.

(224) Sarma PK, Misra R, Aggarwal A. Physical disability, articular, and extra-articular damage in patients with juvenile idiopathic arthritis. Clin Rheumatol 2008;27:1261-1265.

(225) Bromberg MH, Connelly M, Anthony KK, Gil KM, Schanberg LE. Self-reported pain and disease symptoms persist in juvenile idiopathic arthritis despite treatment advances: an electronic diary study. Arthritis Rheumatol 2014;66:462-469.

(226) Lee RR, Rashid A, Ghio D, Thomson W, Cordingley L. Chronic Pain Assessments in Children and Adolescents: A Systematic Literature Review of the Selection, Administration, Interpretation, and Reporting of Unidimensional Pain Intensity Scales. Pain Res Manag 2017;2017:7603758.

(227) Zeltzer L, Bursch B, Walco G. Pain responsiveness and chronic pain: a psychobiological perspective. J Dev Behav Pediatr 1997;18:413-422.

(228) Morton NS. Pain assessment in children. Paediatr Anaesth 1997;7:267-272.

(229) Varni JW, Seid M, Smith KT, Burwinkle T, Brown J, Szer IS. The PedsQL in pediatric rheumatology: reliability, validity, and responsiveness of the Pediatric Quality of Life Inventory Generic Core Scales and Rheumatology Module. Arthritis Rheum 2002;46:714-725.

(230) Manczak M, Rutkowska-Sak L, Raciborski F. Health-related quality of life in children with juvenile idiopathic arthritis - child's and parent's point of view. Reumatologia 2016;54:243-250.

(231) healthactchq ltd. Child Health Questionnaire (CHQ) Scoring and Interpretation Manual. 2017.

(232) Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658-666.

(233)  Ruperto N, Giannini EH. Redundancy of conventional articular response variables used in juvenile chronic arthritis clinical trials. Ann Rheum Dis 1996;55:73-75.

(234)  Ravelli A, Viola S, Ruperto N, Corsi B, Ballardini G, Martini A. Correlation between conventional disease activity measures in juvenile chronic arthritis. Ann Rheum Dis 1997;56:197-200.

(235)  Bazso A, Consolaro, Ruperto N, Pistorio A, Viola S, Magni-Manzoni S et al. Development and testing of reduced joint counts in juvenile idiopathic arthritis. J Rheumatol 2009;36:183-90.

(236)  Consolaro A, Giancane G, Schiappapietra B, Davi S, Calandra S, Lanni S et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2016;14:23.

(237)  Wallace CA, Ruperto N, Giannini EH. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. Journal of Rheumatology 2004;31:2290-2294.

(238)  Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005;52:3554-3562.

(239)  Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007;56:3096-3106.

(240)  Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: Defining criteria based on the juvenile arthritis disease activity score. Arthritis and Rheumatism 2012;64:2366-2374.

(241)  Solari N, Viola S, Pistorio A, Magni-Manzoni S, Vitale R, Ruperto N et al. Assessing current outcomes of juvenile idiopathic arthritis: a cross-sectional study in a tertiary center sample. Arthritis Rheum 2008;59:1571-1579.

(242)  STEINBROCKER O, TRAEGER CH, BATTERMAN RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 1949;140:659-662.

(243)  Poznanski AK, Hernandez RJ, Guire KE, Bereza UL, Garn SM. Carpal length in children--a useful measurement in the diagnosis of rheumatoid arthritis and some concenital malformation syndromes. Radiology 1978;129:661-668.

(244)  Viola S, Felici E, Magni-Manzoni S, Pistorio A, Buoncompagni A, Ruperto N et al. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. Arthritis Rheum 2005;52:2092-2102.

(245)  Landgraf JM, Abetz L, Ware JE. CHQ user's manual. 1 ed. The Health Institute, New England Medical Center, 1996.

(246)  Ravelli A, Ioseliani M, Norambuena X, Sato J, Pistorio A, Rossi F et al. Adapted versions of the Sharp/van der Heijde score are reliable and valid for assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 2007;56:3087-3095.

(247)  Consolaro A, Negro G, Solari N. Targeting remission in juvenile idiopathic arthritis in routine clinical care: experience in 175 newly-diagnosed patients [abstract]. Arthritis Rheum 2012;64:S503.

(248)  Ruperto N, Ravelli A, Pistorio A, Malattia C, Viola S, Cavuto S et al. The Italian version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol 2001;19:S91-S95.

(249)  Magni-Manzoni S, Rossi F, Pistorio A, Temporini F, Viola S, Beluffi G et al. Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. Arthritis Rheum 2003;48:3509-3517.

(250) Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C, Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. J Rheumatol 2003;30:579-584.

(251) Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002;29:1989-1999.

(252) Magni-Manzoni S, Ruperto N, Pistorio A, Sala E, Solari N, Palmisani E et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Care and Research 2008;59:1120-1127.

(253) Adib N, Silman A, Thomson W. Outcome following onset of juvenile idiopathic inflammatory arthritis: I. frequency of different outcomes. Rheumatology (Oxford) 2005;44:995-1001.

(254) Ravelli A, Martini A. Remission in juvenile idiopathic arthritis. Clin Exp Rheumatol 2006;24:S105-S110.

(255) Gare BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. I. Onset and disease process. J Rheumatol 1995;22:295-307.

(256) Arguedas O, Fasth A, Andersson-Gare B. A prospective population based study on outcome of juvenile chronic arthritis in Costa Rica. J Rheumatol 2002;29:174-183.

(257) Bertilsson L, Andersson-Gare B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol 2013;40:715-724.

(258) Vilaiyuk S, Soponkanaporn S, Jaovisidha S, Benjaponpitak S, Manuyakorn W. A retrospective study on 158 Thai patients with juvenile idiopathic arthritis followed in a single center over a 15-year period. Int J Rheum Dis 2016;19:1342-1350.

(259) Pongpanich B, Daengroongroj P. Juvenile rheumatoid arthritis: clinical characteristics in 100 Thai patients. Clin Rheumatol 1988;7:257-261.

(260) Savolainen HA, Lehtimaki M, Kautiainen H, Aho K, Anttila P. HLA B27: a prognostic factor in juvenile chronic arthritis. Clin Rheumatol 1998;17:121-124.

(261) Guillaume S, Prieur AM, Coste J, Job-Deslandre C. Long-term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis. Arthritis Rheum 2000;43:1858-1865.

(262) Svantesson H, Akesson A, Eberhardt K, Elborgh R. Prognosis in juvenile rheumatoid arthritis with systemic onset. A follow-up study. Scand J Rheumatol 1983;12:139-144.

(263) Oliveira-Ramos F, Eusebio M, Martins M, Mourao AF, Furtado C, Campanilho-Marques R et al. Juvenile idiopathic arthritis in adulthood: fulfilment of classification criteria for adult rheumatic diseases, long-term outcomes and predictors of inactive disease, functional status and damage. RMD Open 2016;2:e000304.

(264) Minden K, Kiessling U, Listing J, Niewerth M, Doring E, Meincke J et al. Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. J Rheumatol 2000;27:2256-2263.

(265) Flato B, Lien G, Smerdel A, Vinje O, Dale K, Johnston V et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003;30:386-393.

(266) Hertzberger-ten CR, de Vries-van der Vlugt BC, van Suijlekom-Smit LW, Cats A. Disease patterns in early onset pauciarticular juvenile chronic arthritis. Eur J Pediatr 1992;151:339-341.

(267) Al-Matar MJ, Petty RE, Tucker LB, Malleson PN, Schroeder ML, Cabral DA. The early pattern of joint involvement predicts disease progression in children with oligoarticular (pauciarticular) juvenile rheumatoid arthritis. Arthritis Rheum 2002;46:2708-2715.

(268) Kotaniemi K, Kotaniemi A, Savolainen A. Uveitis as a marker of active arthritis in 372 patients with juvenile idiopathic seronegative oligoarthritis or polyarthritis. Clin Exp Rheumatol 2002;20:109-112.

(269) Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis and Rheumatism 2005;52:3554-3562.

(270) Flato B, Hoffmann-Vold AM, Reiff A, Forre O, Lien G, Vinje O. Long-term outcome and prognostic factors in enthesitis-related arthritis: a case-control study. Arthritis Rheum 2006;54:3573-3582.

(271) Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. Arthritis Rheum 2006;54:1595-1601.

(272) Fernandes TAP, Corrente JE, Magalhaes CS. Remission status follow-up in children with juvenile idiopathic arthritis. J Pediatr (Rio J) 2007;83:141-148.

(273) Oen K, Tucker L, Huber AM, Miettunen P, Scuccimarri R, Campillo S et al. Predictors of early inactive disease in a juvenile idiopathic arthritis cohort: results of a Canadian multicenter, prospective inception cohort study. Arthritis Rheum 2009;61:1077-1086.

(274) Albers HM, Brinkman DMC, Kamphuis SSM, van Suijlekom-Smit LWA, van Rossum MAJ, Hoppenreijs EPAH et al. Clinical course and prognostic value of disease activity in the first two years in different subtypes of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2010;62:204-212.

(275) Nordal E, Zak M, Aalto K, Berntson L, Fasth A, Herlin T et al. Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:2809-2818.

(276) Berntson L, Nordal E, Aalto K, Peltoniemi S, Herlin T, Zak M et al. HLA-B27 predicts a more chronic disease course in an 8-year followup cohort of patients with juvenile idiopathic arthritis. J Rheumatol 2013;40:725-31.

(277) Huang H, Qian X, Yu H, Li J, Zhang Y. Clinical analysis in 202 children with juvenile idiopathic arthritis. Clin Rheumatol 2013;32:1021-1027.

(278) Russo RA, Katsicas MM. Patients with very early-onset systemic juvenile idiopathic arthritis exhibit more inflammatory features and a worse outcome. J Rheumatol 2013;40:329-334.

(279) Albers HM, Reinards TH, Brinkman DM, Kamphuis SS, Van Rossum MA, Hoppenreijs EP et al. Genetic variation in VTCN1 (B7-H4) is associated with course of disease in juvenile idiopathic arthritis. Ann Rheum Dis 2014;73:1198-1201.

(280) Berntson L, Nordal E, Fasth A, Aalto K, Herlin T, Nielsen S et al. Anti-type II collagen antibodies, anti-CCP, IgA RF and IgM RF are associated with joint damage, assessed eight years after onset of juvenile idiopathic arthritis (JIA). Pediatr Rheumatol Online J 2014;12:22.

(281) Selvaag AM, Aulie HA, Lilleby V, Flato B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. Ann Rheum Dis 2014.

(282) Sengler C, Klotsche J, Niewerth M, Liedmann I, Foll D, Heiligenhaus A et al. The majority of newly diagnosed patients with juvenile idiopathic arthritis reach an inactive disease state within the first year of specialised care: data from a German inception cohort. RMD Open 2015;1:e000074.

(283) Alberdi-Saugstrup M, Zak M, Nielsen S, Herlin T, Nordal E, Berntson L et al. High-sensitive CRP as a predictive marker of long-term outcome in juvenile idiopathic arthritis. Rheumatol Int 2017;37:695-703.

(284) Glerup M, Herlin T, Twilt M. Remission rate is not dependent on the presence of antinuclear antibodies in juvenile idiopathic arthritis. Clin Rheumatol 2017;36:671-676.

(285) Verstappen SM, Cobb J, Foster HE, Fu B, Baildam E, Wedderburn LR et al. The association between low socioeconomic status with high physical limitations and low illness self-perception in patients with juvenile idiopathic arthritis: results from the Childhood Arthritis Prospective Study. Arthritis Care Res (Hoboken ) 2015;67:382-389.

(286) Esbjornsson AC, Aalto K, Brostrom EW, Fasth A, Herlin T, Nielsen S et al. Ankle arthritis predicts polyarticular disease course and unfavourable outcome in children with juvenile idiopathic arthritis. Clin Exp Rheumatol 2015;33:751-757.

(287) Berntson L, Nordal E, Aalto K, Peltoniemi S, Herlin T, Zak M et al. HLA-B27 predicts a more chronic disease course in an 8-year followup cohort of patients with juvenile idiopathic arthritis. J Rheumatol 2013;40:725-731.

(288) Guzman J, Henrey A, Loughin T, Berard RA, Shiff NJ, Jurencak R et al. Predicting Which Children with Juvenile Idiopathic Arthritis Will Have a Severe Disease Course: Results from the ReACCh-Out Cohort. J Rheumatol 2016.

(289) Nordal EB, Zak M, Aalto K, Berntson L, Fasth A, Herlin T et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis 2012;71:1122-1127.

(290) O'Dell JR. Treating rheumatoid arthritis early: a window of opportunity? Arthritis Rheum 2002;46:283-285.

(291) Woo P. Theoretical and practical basis for early aggressive therapy in paediatric autoimmune disorders. Curr Opin Rheumatol 2009;21:552-557.

(292) Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000;43:22-29.

(293) Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol 2003;21:S154-S157.

(294) Sherry DD, Stein LD, Reed AM, Schanberg LE, Kredich DW. Prevention of leg length discrepancy in young children with pauciarticular juvenile rheumatoid arthritis by treatment with intraarticular steroids. Arthritis Rheum 1999;42:2330-2334.

(295) Albers HM, Wessels JA, van der Straaten RJ, Brinkman DM, Suijlekom-Smit LW, Kamphuis SS et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum 2009;61:46-51.

(296) Bartoli M, Taro M, Magni-Manzoni S, Pistorio A, Traverso F, Viola S et al. The magnitude of early response to methotrexate therapy predicts long-term outcome of patients with juvenile idiopathic arthritis. Ann Rheum Dis 2008;67:370-374.

(297) Beukelman T, Anink J, Berntson L, Duffy C, Ellis JA, Glerup M et al. A survey of national and multi-national registries and cohort studies in juvenile idiopathic arthritis: challenges and opportunities. Pediatr Rheumatol Online J 2017;15:31.

(298) Coggon D, Rose G, Barker DJP. Measurement error and bias. Epidemiology for the Uninitiated. The BMJ, 2003.

(299) Berk RA. An Introduction to Sample Selection Bias in Sociological Data. American Sociological Review 1983;48:386-398.

(300) Kukull WA, Ganguli M. Generalizability. Neurology 2012;78:1886-1891.

(301) Bellomo R, Warrillow SJ, Reade MC. Why we should be wary of single-center trials. Crit Care Med 2009;37:3114-3119.

(302) Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer 2008;112:228-242.

(303) Bonevski B, Randell M, Paul C, Chapman K, Twyman L, Bryant J et al. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. BMC Med Res Methodol 2014;14:42.

(304) Giuliano AR, Mokuau N, Hughes C, Tortolero-Luna G, Risendal B, Ho RCS et al. Participation of minorities in cancer research: the influence of structural, cultural, and linguistic factors. Ann Epidemiol 2000;10:S22-S34.

(305) Miranda J, Azocar F, Organista KC, Munoz RF, Lieberman A. Recruiting and retaining low-income Latinos in psychotherapy research. J Consult Clin Psychol 1996;64:868-874.

(306) Ejiogu N, Norbeck JH, Mason MA, Cromwell BC, Zonderman AB, Evans MK. Recruitment and retention strategies for minority or poor clinical research participants: lessons from the Healthy Aging in Neighborhoods of Diversity across the Life Span study. Gerontologist 2011;51 Suppl 1:S33-S45.

(307) Etikan I, Musa AM, Alkassim RS. Comparison of Convenience Sampling and Purposive Sampling. American Journal of Theoretical and Applied Statistics 2016;5:1-4.

(308) Kendall JM. Designing a research project: randomised controlled trials and their principles. Emerg Med J 2003;20:164-168.

(309) Suresh K, Thomas SV, Suresh G. Design, data analysis and sampling techniques for clinical research. Ann Indian Acad Neurol 2011;14:287-290.

(310) Bernard TJ, Armstrong-Wells J, Goldenberg NA. The institution-based prospective inception cohort study: design, implementation, and quality assurance in pediatric thrombosis and stroke research. Semin Thromb Hemost 2013;39:10-14.

(311) Pourhoseingholi MA, Baghestani AR, Vahedi M. How to control confounding effects by statistical analysis. Gastroenterol Hepatol Bed Bench 2012;5:79-83.

(312) Greenland S, Morgenstern H. Confounding in health research. Annu Rev Public Health 2001;22:189-212.

(313) Lieber RL. Statistical significance and statistical power in hypothesis testing. J Orthop Res 1990;8:304-309.

(314) Fitzmaurice G. Confounding: Regression adjustment. Nutrition 2006;22:581-583.

(315) Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol 1995;48:1495-1501.

(316) Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-1379.

(317) Austin PC, Steyerberg EW. The number of subjects per variable required in linear regression analyses. J Clin Epidemiol 2015;68:627-636.

(318) Walter S, Tiemeier H. Variable selection: current practice in epidemiological studies. Eur J Epidemiol 2009;24:733-736.

(319) Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340-349.

(320) Harrell FE. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer, 2001.

(321) Karahalios A, Baglietto L, Carlin JB, English DR, Simpson JA. A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures. BMC Med Res Methodol 2012;12:96.

(322)  Little RJA, Rubin DM. Statistical analysis with missing data. New York: John Wiley and Sons, 1987.

(323)  Hardy SE, Allore H, Studenski SA. Missing data: a special challenge in aging research. J Am Geriatr Soc 2009;57:722-729.

(324)  Streiner D, Geddes J. Intention to treat analysis in clinical trials when there are missing data. Evid Based Ment Health 2001;4:70-71.

(325)  Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.

(326)  Steyerberg EW, van VM. Imputation is beneficial for handling missing data in predictive models. J Clin Epidemiol 2007;60:979.

(327)  Zhang Z. Missing data imputation: focusing on single imputation. Ann Transl Med 2016;4:9.

(328)  Molenberghs G, Fitzmaurice G, Kenward MG, Tsiatis A, Verbeke G. Handbook of Missing Data Methodology. Florida: Chapman & Hall/CRC, 2014.

(329)  Saha C, Jones MP. Bias in the last observation carried forward method under informative dropout. Journal of Statistical Planning and Inference 2009;139:246-255.

(330)  Molnar FJ, Hutton B, Fergusson D. Does analysis using "last observation carried forward" introduce bias in dementia research? CMAJ 2008;179:751-753.

(331)  Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple Imputation by Chained Equations: What is it and how does it work? Int J Methods Psychiatr Res 2011;20:40-49.

(332)  Horton NJ, Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. Am Stat 2007;61:79-90.

(333)  Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57.

(334)  Schafer JL, Olsen MK. Multiple Imputation for Multivariate Missing-Data Problems: A Data Analyst's Perspective. Multivariate Behav Res 1998;33:545-571.

(335)  Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley, 1987.

(336)  Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. Prev Sci 2007;8:206-213.

(337)  Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychol Methods 2001;6:330-351.

(338)  Leacy FP, Floyd S, Yates TA, White IR. Analyses of Sensitivity to the Missing-at-Random Assumption Using Multiple Imputation With Delta Adjustment: Application to a Tuberculosis/HIV Prevalence Survey With Incomplete HIV-Status Data. Am J Epidemiol 2017;185:304-315.

(339)  McCluskey A, Lalkhen AG. Statistics II: Central tendency and spread of data. Continuing Education in Anaesthesia Critical Care & Pain 2007;7:127-130.

(340)  McCluskey A, Lalkhen AG. Statistics I: data and correlations. Continuing Education in Anaesthesia Critical Care & Pain 2007;7:95-99.

(341)  Casson RJ, Farmer LD. Understanding and checking the assumptions of linear regression: a primer for medical researchers. Clin Exp Ophthalmol 2014;42:590-596.

(342)  Bewick V, Cheek L, Ball J. Statistics review 14: Logistic regression. Crit Care 2005;9:112-118.

(343) Salehi M, Roudbari M. Zero inflated Poisson and negative binomial regression models: application in education. Med J Islam Repub Iran 2015;29:297.

(344) Hayat MJ, Higgins M. Understanding poisson regression. J Nurs Educ 2014;53:207-215.

(345) Yang Z, Hardin JW, Addy CL. Testing overdispersion in the zero-inflated Poisson model. Journal of Statistical Planning and Inference 2009;139:3340-3353.

(346) Barker LE, Shaq KM. Best (but of t-forgotten) practices: checking assumptions concerning regression residual. Am J Clin Nutr 2016;102:533-539.

(347) McNeish D, Stapleton LM. Modeling Clustered Data with Very Few Clusters. Multivariate Behav Res 2016;51:495-518.

(348) Austin PC, Goel V, van WC. An introduction to multilevel regression models. Can J Public Health 2001;92:150-154.

(349) Alexopoulos EC. Introduction to Multivariate Regression Analysis. Hippokratia 2010;14:23-28.

(350) Yoo W, Mayberry R, Bae S, Singh K, He Q, Lillard Jr JW. A Study of Effects of MultiCollinearity in the Multivariable Analysis. Int J Appl Sci Technol 2015;4:9-19.

(351) Dimopoulou D, Trachana M, Pratsidou-Gertsi P, Sidiropoulos P, Kanakoudi-Tsakalidou F, Dimitroulas T et al. Predictors and long-term outcome in Greek adults with juvenile idiopathic arthritis: a 17-year continuous follow-up study. Rheumatology (Oxford) 2017;56:1928-1938.

(352) Hullmann SE, Ryan JL, Ramsey RR, Chaney JM, Mullins LL. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). Arthritis Care Res (Hoboken ) 2011;63 Suppl 11:S420-S430.

(353) Consolaro A, Vitale R, Pistorio A, Lattanzi B, Ruperto N, Malattia C et al. Physicians' and parents' ratings of inactive disease are frequently discordant in juvenile idiopathic arthritis. J Rheumatol 2007;34:1773-1776.

(354) Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-778.

(355) Shenoi S, Wallace CA. Remission in juvenile idiopathic arthritis: current facts. Curr Rheumatol Rep 2010;12:80-86.

(356) Wood P. Special Meeting on: Nomenclature and Classification of Arthritis in Children. The Care of Rheumatic Children , 47-50. 1978.

(357) Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9, W64.

(358) Selvaag AM, Lien G, Sorskaar D, Vinje O, Forre O, Flato B. Early disease course and predictors of disability in juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3 year prospective study. J Rheumatol 2005;32:1122-1130.

(359) Gare BA, Fasth A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. Pediatrics 1992;90:950-958.

(360) Pasma A, van't Spijker A, Hazes JM, Busschbach JJ, Luime JJ. Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: a systematic review. Semin Arthritis Rheum 2013;43:18-28.

(361) The Cochrane Collaboration. The Cochrane Collaboration's tool for assessing risk of bias. 2011.

(362) Shen CC, Yao TC, Yeh KW, Huang JL. Association of disease activity and anti-rheumatic treatment in juvenile idiopathic arthritis with serum lipid profiles: a prospective study. Semin Arthritis Rheum 2013;42:590-596.

(363) Bertilsson L, Andersson-Gare B, Fasth A, Forsblad-d'Elia H. A 5-year prospective population-based study of juvenile chronic arthritis: onset, disease process, and outcome. Scand J Rheumatol 2012;41:379-382.

(364) Berntson L, Wernroth L, Fasth A, Aalto K, Herlin T, Nielsen S et al. Assessment of disease activity in juvenile idiopathic arthritis. The number and the size of joints matter. J Rheumatol 2007;34:2106-2111.

(365) Gare BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. II. Outcome. J Rheumatol 1995;22:308-319.

(366) Gare BA, Fasth A, Wiklund I. Measurement of functional status in juvenile chronic arthritis: evaluation of a Swedish version of the Childhood Health Assessment Questionnaire. Clin Exp Rheumatol 1993;11:569-576.

(367) Padeh S, Farzam N, Chayen G, Gerstein M, Berkun Y. Pentraxin 3 is a marker of early joint inflammation in patients with juvenile idiopathic arthritis. Immunol Res 2013;56:444-450.

(368) Selvaag AM, Flato B, Dale K, Lien G, Vinje O, Smerdel-Ramoya A et al. Radiographic and clinical outcome in early juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3-year prospective study. J Rheumatol 2006;33:1382-1391.

(369) Flato B, Aasland A, Vinje O, Forre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. J Rheumatol 1998;25:366-375.

(370) Wallace CA, Ravelli A, Huang B, Giannini EH. Preliminary validation of clinical remission criteria using the OMERACT filter for select categories of juvenile idiopathic arthritis. Journal of Rheumatology 2006;33:789-795.

(371) Chang CY, Meyer RM, Reiff AO. Impact of Medication Withdrawal Method on Flare-free Survival in Patients with Juvenile Idiopathic Arthritis on Combination Therapy. Arthritis Care Res (Hoboken) 2014;12: doi: 10.1002/acr.22477.

(372) Wallace CA. Current management of juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol 2006;20:279-300.

(373) Flato B, Lien G, Smerdel-Ramoya A, Vinje O. Juvenile psoriatic arthritis: longterm outcome and differentiation from other subtypes of juvenile idiopathic arthritis. J Rheumatol 2009;36:642-650.

(374) British Society for Paediatric and Adolescent Rheumatology. Standards of Care for children and young people with Juvenile Idiopathic Arthritis. 2010.

(375) Neogi T, Felson DT. Composite versus individual measures of disease activity in rheumatoid arthritis. J Rheumatol 2008;35:185-187.

(376) Ringold S, Ward TM, Wallace CA. Disease activity and fatigue in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2013;65:391-397.

(377) Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, van ZD, Kerstens PJ, Hazes JM et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381-3390.

(378) Egsmose C, Lund B, Borg G, Pettersson H, Berg E, Brodin U et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. J Rheumatol 1995;22:2208-2213.

(379) Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-451.

(380) Finckh A, Liang MH, van Herckenrode CM, de PP. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55:864-872.

(381) Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-516.

(382) Adib N, Hyrich K, Thornton J, Lunt M, Davidson J, Gardner-Medwin J et al. Association between duration of symptoms and severity of disease at first presentation to paediatric rheumatology: results from the Childhood Arthritis Prospective Study. Rheumatology (Oxford) 2008;47:991-995.

(383) Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3-15.

(384) Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016;75:16-22.

(385) Consolaro A, Negro G, Lanni S, Solari N, Martini A, Ravelli A. Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. Clinical and experimental rheumatology 2012;30:S157-S162.

(386) Consolaro A, Calandra S, Robbiano C, Ravelli A. Treating Juvenile Idiopathic Arthritis According to JADAS-Based Targets. Ann Paediatr Rheum 3[1], 4-10. 2014.

(387) Wallace CA. Developing standards of care for patients with juvenile idiopathic arthritis. Rheumatology (Oxford) 2010;49:1213-1214.

(388) Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin M et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis 2011;70:1605-12.

(389) Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum 2012;64:2012-2021.

(390) Ravelli A, Viola S, Ruperto N, Corsi B, Ballardini G, Martini A. Correlation between conventional disease activity measures in juvenile chronic arthritis. Ann Rheum Dis 1997;56:197-200.

(391) Armbrust W, Kaak JG, Bouma J, Lelieveld OT, Wulffraat NM, Sauer PJ et al. Assessment of disease activity by patients with juvenile idiopathic arthritis and the parents compared to the assessment by pediatric rheumatologists. Pediatr Rheumatol Online J 2013;11:48.

(392) Anink J, Dolman KM, Merlijn van den Berg J, van Veenendaal M, Kuijpers TW, van Rossum MAJ. Two-year outcome of juvenile idiopathic arthritis in current daily practice: what can we tell our patients? Clin Exp Rheumatol 2012;30:972-978.

(393) McErlane F, Foster HE, Carrasco R, Baildam EM, Chieng SE, Davidson JE et al. Trends in paediatric rheumatology referral times and disease activity indices over a ten-year period among children and young people with Juvenile Idiopathic Arthritis: results from the childhood arthritis prospective Study. Rheumatology (Oxford) 2016;55:1225-1234.

(394) Lurati A, Salmaso A, Gerloni V, Gattinara M, Fantini F. Accuracy of Wallace criteria for clinical remission in juvenile idiopathic arthritis: a cohort study of 761 consecutive cases. J Rheumatol 2009;36:1532-1535.

(395) Consolaro A, Giancane G, Schiappapietra B, Davi S, Calandra S, Lanni S et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatric Rheumatology Online Journal 2016;14.

(396) Davies K, , Cleary G, , Foster H,  et al. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology 2010;49:1406-1408.

(397) Shoop-Worrall SJW, Kearsley-Fleet L, Thomson W, Verstappen SMM, Hyrich KL. How common is remission in juvenile idiopathic arthritis: A systematic review. Semin Arthritis Rheum 2017.

(398) Shoop-Worrall SJ, Verstappen SM, Baildam E, Chieng A, Davidson J, Foster H et al. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. Ann Rheum Dis 2017.

(399) Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L et al. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol 2001;19:S1-S9.

(400) Hullmann SE, Ryan JL, Ramsey RR, Chaney JM, Mullins LL. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). Arthritis Care Res (Hoboken ) 2011;63 Suppl 11:S420-S430.

(401) Consolaro A, Vitale R, Pistorio A, Lattanzi B, Ruperto N, Malattia C et al. Physicians' and parents' ratings of inactive disease are frequently discordant in juvenile idiopathic arthritis. J Rheumatol 2007;34:1773-1776.

(402) Ruperto N, Lovell DJ, Li T, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken ) 2010;62:1542-1551.

(403) Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Perez N, Silva CA et al. Long-term safety, efficacy, and quality of life in patients with juvenile idiopathic arthritis treated with intravenous abatacept for up to seven years. Arthritis Rheumatol 2015;67:2759-2770.

(404) Prince FH, Geerdink LM, Borsboom GJ, Twilt M, van Rossum MA, Hoppenreijs EP et al. Major improvements in health-related quality of life during the use of etanercept in patients with previously refractory juvenile idiopathic arthritis. Ann Rheum Dis 2010;69:138-142.

(405) Cespedes-Cruz A, Gutierrez-Suarez R, Pistorio A, Ravelli A, Loy A, Murray KJ et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. Ann Rheum Dis 2008;67:309-314.

(406) Klotsche J, Minden K, Thon A, Ganser G, Urban A, Horneff G. Improvement in health-related quality of life for children with juvenile idiopathic arthritis after start of treatment with etanercept. Arthritis Care and Research 2014;66:253-262.

(407) Halbig M, Horneff G. Improvement of functional ability in children with juvenile idiopathic arthritis by treatment with etanercept. Rheumatol Int 2009;30:229-238.

(408) Beresford MW. Juvenile idiopathic arthritis: New insights into classification, measures of outcome, and pharmacotherapy. Pediatric Drugs 2011;13:161-173.

(409) Shoop-Worrall SJW, Kearsley-Fleet L, Thomson W, Verstappen SMM, Hyrich KL. How common is remission in juvenile idiopathic arthritis: A systematic review. Semin Arthritis Rheum 2017;47:331-337.

(410) Shoop-Worrall SJ, Verstappen SM, Baildam E, Chieng A, Davidson J, Foster H et al. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. Ann Rheum Dis 2017.

(411) Shoop-Worrall SJ, Verstappen SM, McDonagh JE, Baildam E, Chieng A, Davidson J et al. Long term outcomes following achievement of clinically inactive disease in juvenile idiopathic arthritis: the importance of definition. Arthritis Rheumatol 2018.

(412) Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS et al. Clinically inactive disease in a cohort of children with new-onset polyarticular juvenile idiopathic arthritis treated with early aggressive therapy: time to achievement, total duration, and predictors. J Rheumatol 2014;41:1163-1170.

(413) Glerup M, Herlin T, Twilt M. Clinical Outcome and Long-term Remission in JIA. Curr Rheumatol Rep 2017;19:75.

(414) Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis. Arthritis & Rheumatism 2013;65:2499-2512.

(415) van Dijkhuizen EH, Wulffraat NM. Early predictors of prognosis in juvenile idiopathic arthritis: a systematic literature review. Ann Rheum Dis 2015;74:1996-2005.

(416) Verstappen SMM. The impact of socio-economic status in rheumatoid arthritis. Rheumatology 56[1], 1051-1052. 2017.

(417) Joplin S, van der Zwan R, Joshua F, Wong PK. Medication adherence in patients with rheumatoid arthritis: the effect of patient education, health literacy, and musculoskeletal ultrasound. Biomed Res Int 2015;2015:150658.

(418) Elbinoune I, Amine B, Rostom S, Shyen S, Elbadri D, Ezzahri M et al. Discordance Between Physician's and Parent's Global Assessments in Juvenile Idiopathic Arthritis. Annals of Paediatric Rheumatology 5, 71-78. 2016.

(419) Lavallee DC, Chenok KE, Love RM, Petersen C, Holve E, Segal CD et al. Incorporating Patient-Reported Outcomes Into Health Care To Engage Patients And Enhance Care. Health Aff (Millwood ) 2016;35:575-582.

(420) Weitzman ER, Wisk LE, Salimian PK, Magane KM, Dedeoglu F, Hersh AO et al. Adding patient-reported outcomes to a multisite registry to quantify quality of life and experiences of disease and treatment for youth with juvenile idiopathic arthritis. Journal of Patient-Reported Outcomes 2017;2.

(421) Filocamo G, Davi S, Pistorio A, Bertamino M, Ruperto N, Lattanzi B et al. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. J Rheumatol 2010;37:1534-1541.

(422) Shiff NJ, Tupper S, Oen K, Guzman J, Lim H, Lee CH et al. Trajectories of pain severity in juvenile idiopathic arthritis: results from the Research in Arthritis in Canadian Children Emphasizing Outcomes cohort. Pain 2017.

(423) Rashid A, Cordingley L, Carrasco R, Foster HE, Baildam EM, Chieng A et al. Patterns of pain over time among children with juvenile idiopathic arthritis. Arch Dis Child 2017.

(424) Shaw KL, Southwood TR, McDonagh JE. Growing up and moving on in rheumatology: parents as proxies of adolescents with juvenile idiopathic arthritis. Arthritis Rheum 2006;55:189-198.

(425) Brunner HI, Klein-Gitelman MS, Miller MJ, Barron A, Baldwin N, Trombley M et al. Minimal clinically important differences of the childhood health assessment questionnaire. J Rheumatol 2005;32:150-161.

(426) Quay TA, Frimer L, Janssen PA, Lamers Y. Barriers and facilitators to recruitment of South Asians to health research: a scoping review. BMJ Open 2017;7:e014889.

(427) Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. JAMA 2004;292:1593-1601.

(428)    Office for National Statistics. PEED, Current Estimates, Population Estimates by Ethnic Group Mid-2009. 2011.

(429)    Scotland's Census 2011. Ethnic group by sex by age. Scotland's Census 2011 - National Records of Scotland . 2014.

(430)    Malattia C, Martini A. Juvenile Idiopathic Arthritis. The Autoimmune Diseases. Academic Press, Elsevier, 2014:525-536.

(431)    Prahalad S, Glass DN. Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis? Arthritis Res 2002;4:303-310.

(432)    Cobb JE, Hinks A, Thomson W. The genetics of juvenile idiopathic arthritis: current understanding and future prospects. Rheumatology (Oxford) 2014;53:592-599.

(433)    Weiss PF. Diagnosis and treatment of enthesitis-related arthritis. Adolesc Health Med Ther 2012;2012:67-74.

(434)    Hinks A, Bowes J, Cobb J, Ainsworth HC, Marion MC, Comeau ME et al. Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritic diseases. Ann Rheum Dis 2017;76:765-772.

(435)    Davies R, Southwood TR, Kearsley-Fleet L, Lunt M, Hyrich KL. Medically Significant Infections Are Increased in Patients With Juvenile Idiopathic Arthritis Treated With Etanercept: Results From the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. Arthritis Rheumatol 2015;67:2487-2494.

(436)    Horneff G. Safety of biologic therapies for the treatment of juvenile idiopathic arthritis. Expert Opin Drug Saf 2015;14:1111-1126.

(437)    Health and Social Care Information Centre. Prescribing Costs in Hospitals and the Community; England 2015/16. NHS Digital, editor. 2016.

(438)    NHS England. Commissioning framework for biological medicines. 2017.

(439)    Simpson K, Marlow N, Shaw J, Rudakova A. Pharmacoeconomic issues of adalimumab therapy in juvenile idiopathic arthritis. Pediatr Pharmacol 2012;9:48-52.

(440)    Cummins C, Connock M, Fry-Smith A, Burls A. A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept. Health Technol Assess 2002;6:1-43.

(441)    Decock D, Davies R, Kearsley-Fleet L, Baildam E, Beresford MW, Foster H et al. Biosimilar use in children and young people with juvenile idiopathic arthritis in a real-world setting in the United Kingdom. Rheumatology 57[Suppl 8]. 2018.

(442)    Kay J, Schoels MM, Dorner T, Emery P, Kvien TK, Smolen JS et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis 2018;77:165-174.

(443)    Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-977.

(444)    Armitt G, Cobb J, Shoop S, Rashid A, Sampath S, the CAPTURE-JIA Expert Group et al. CAPTURE-JIA Patient Status Dataset: a consensus-derived core dataset to improve clinical care for children and young people with Juvenile Idiopathic Arthritis. Proceedings of the British Society for Adolescentand Paediatric Rheumatology Annual Conference , 25-26. 2015.

(445)    Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van ST et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827-836.

(446)    Williams JG, Mann RY. Hospital episode statistics: time for clinicians to get involved? Clin Med (Lond) 2002;2:34-37.

(447)    Beukenhorst AL, Sergeant JC, Little MA, McBeth J, Dixon WG. Consumer Smartwatches for Collecting Self-Report and Sensor Data: App Design and Engagement. Stud Health Technol Inform 2018;247:291-295.

(448)    Reade S, Spencer K, Sergeant JC, Sperrin M, Schultz DM, Ainsworth J et al. Cloudy with a Chance of Pain: Engagement and Subsequent Attrition of Daily Data Entry in a Smartphone Pilot Study Tracking Weather, Disease Severity, and Physical Activity in Patients With Rheumatoid Arthritis. JMIR Mhealth Uhealth 2017;5:e37.

(449)    Sharp CA, Austin L, Machin M, Humphreys J, Mellor P, McCarthy J et al. Sharing the burden of rheumatoid arthritis through remote monitoring of rheumatoid arthritis (REMORA): implications for patients and clinicians. Annals of the Rheumatic Diseases 77, 552-553. 2018.

(450)    Martinez-Perez B, de lT-D, I, Lopez-Coronado M. Mobile health applications for the most prevalent conditions by the World Health Organization: review and analysis. J Med Internet Res 2013;15:e120.

(451)    Boulos MN, Brewer AC, Karimkhani C, Buller DB, Dellavalle RP. Mobile medical and health apps: state of the art, concerns, regulatory control and certification. Online J Public Health Inform 2014;5:229.

(452)    Druce KL, McBeth J, van der Veer SN, Selby DA, Vidgen B, Georgatzis K et al. Recruitment and Ongoing Engagement in a UK Smartphone Study Examining the Association Between Weather and Pain: Cohort Study. JMIR Mhealth Uhealth 2017;5:e168.

(453)    Choi HK, Nguyen US, Niu J, Danaei G, Zhang Y. Selection bias in rheumatic disease research. Nat Rev Rheumatol 2014;10:403-412.

# 10 APPENDICES

1.    **Study title**

Childhood Arthritis Prospective Study (CAPS)


2.    **Invitation paragraph**

Your child is being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish.  Ask us if there is anything that is not clear or if you would like more information.  Take time to decide whether or not you wish to take part.

Thank you for reading this.


3.    **What is the purpose of the study?**

Arthritis in children affects around one in a thousand children.  In the majority of cases the cause is unknown.  It is likely that the development of arthritis is related in part to the child's genetic make-up and in part to other factors such as infection or other illnesses. The arthritis may go away after some months or years or may persist into adult life.  At the moment we cannot predict which children will recover and which children will have more long-term problems.  The aim of the study is to identify factors that may be involved in the development of arthritis and to identify factors that may help in the prediction of the long- term outcome of the illness.

Better understanding of the cause of childhood arthritis may lead to the possibility of prevention of the illness in future.  Better understanding of the course of the illness will help in choosing the best treatment for children in the future.


4.    **Why has my child been chosen?**

We are asking all children who have recently developed arthritis to take part in this study.


5.    **Do we have to take part?**

Your child does not have to take part in this study.  It is up to you to decide whether or not to take part. Your child's treatment will not be affected if you decide not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form.  If you decide to take part you are still free to withdraw at any time and without giving a reason.

6.    **What will happen to my child if he/she takes part?**

(i)    The study will begin as part of a normal visit to the Rheumatology Clinic.   The Hospital Consultant will ask patients and parents whether they are happy to take part in the study.   If you agree then the consultant will send your child's name, address and telephone number to the Research Nurse. The Consultant will also provide details of your child's illness and treatment as well as the results of any blood test or X-rays that have been done as part of the hospital visit.

(ii)   With your help the nurse will complete a form about your child's medical history.. You/your child will be asked to complete some questionnaires about how the arthritis affects your child's daily activities, their moods and how it affects you.  You will also be asked about any family history of arthritis and related conditions.  . Occasionally, these questions may be posed over the telephone or we may post the questionnaires to your home.   Follow-up questionnaires will be sent to you approximately once per year, although these may become less frequent as the study progresses. At this stage we do not know how long in total we will want to collect this information from you/ your child but in the first instance we imagine this will be for at least 10 years.

(iii)  Information regarding your child's health status will also be obtained from the medical case notes.

(iv)   At some point we will ask your child to provide a small blood sample (about one teaspoon). Blood tests are a necessary part of the management of arthritis in children.  The research blood sample will be taken at a time when blood is also needed for routine purposes. Therefore there would be no additional discomfort and no extra risk to the child. If your child does not require a blood sample for routine clinical purposes he/she will be asked to provide a spit sample. The procedure will not cause your child any discomfort. Samples will be sent to the Centre for Musculoskeletal Research Laboratories at the University of Manchester where genetic material (plasma/cells/DNA/RNA) will be extracted. This will be stored under secure conditions until the study is complete.  The material will only be used for research into the genetics of childhood arthritis.  The exact genes to be studied cannot be identified now but will include ones we already know are important in childhood arthritis and ones discovered during the time the study is being done.

(v)    As part of routine clinical care it may be necessary for your child to have some fluid removed from a joint and a joint injection.  This is often done under general anaesthetic.  The fluid removed is usually thrown away.  This fluid may be sent to the Centre for Musculoskeletal Research laboratories for research purposes.   A small (about 1-2 teaspoons) additional blood sample will be taken at the same time for research purposes and also sent to Centre for Musculoskeletal Research laboratories.  Both of these samples will be used to try to identify which genes are causing the joint swelling.

(vi)   The Health and Social Care Information Centre (HSCIC) collects statistics on health outcomes across England in collaboration with the NHS.  Examples of this data include information on any resident of the UK who dies and anybody who develops a cancer. Researchers can "flag" the names of participants involved in their research with the HSCIC such that in the rare event one of these health outcomes occurs, the researchers will be informed. This allows them to have almost 100% complete information on these rare outcomes. With your permission, your child's name would be "flagged" with the HSCIC.  This will allow us to study

very long-term outcomes, far into adulthood, in children who have or have had arthritis.

Data linkage, the process of linking together two or more streams of data, allows researchers to make use of routinely collected data (e.g. when a child is admitted to hospital) that benefits research. With your permission, we would apply to the Health and Social Care Information Centre to link data from the CAPS study with hospital data to provide a more detailed picture of the children's' health outcomes. Any personal data used for linkage will be deleted, to avoid identification.

### 7. What are the possible disadvantages and risks of taking part?

There is no risk associated with taking part in the study and the only inconvenience is the time given to complete the questionnaires. As mentioned above, the research blood sample would be taken at the same time as blood was required for routine testing and so no additional risk would be involved.

### 8. What are the possible benefits of taking part?

The research may not have a direct benefit for your child or the family. However, many families find it helpful to talk about the illness and the impact that it is having on the life of the family with someone who is independent (e.g. a Research Nurse).

### 9. Will my taking part in this study be kept confidential?

The patient's notes are kept confidential as usual at the hospital. Separate research records will be kept by the Research Nurse and only those involved in the study will have access to them. Since this study involves a number of Centres in the United Kingdom, information about your child will be sent to the Centre for Musculoskeletal Research at The University of Manchester. Each participant will be given a code number so that they cannot be identified. All data will be stored on a secure database that can only be looked at by authorised individuals. The individual results from any genetic studies will not be provided to the child, the family, the Consultant or any other organisation or individual. With your permission your child's GP will be notified of their participation in the study.

### 10. What will happen to the results of the research study?

The results of the study will be presented at scientific meeting and published in medical journals but, again, no identifying information will be given in these publications.

### 11. Who is organising and funding the research?

The research is being funded by the Arthritis Research UK and will be organised by the Centre for Musculoskeletal Research at Manchester University.

Your child's consultant will not receive any payment for including and looking after any

patients in the study.

12. **Who has reviewed the study?**

This study has been reviewed by the Northwest Multi Centre Research Ethics Committee.

13. **Contact for Further Information**

If you have any questions about the study please discuss them with Prof. Wendy Thomson or Dr. Kimme Hyrich at the Centre for Musculoskeletal Research, University of Manchester.  Telephone: 0161 275 5037/5040.

If you wish to take part in this study please complete the Consent Forms which you have been given and hand them back to your Consultant/Research Nurse or return to the Centre for Musculoskeletal Research Unit by post.

# Childhood Arthritis Prospective Study (CAPS)

**Information for young children (Guide Age: under 6)**

We would like to ask for your help with our project!
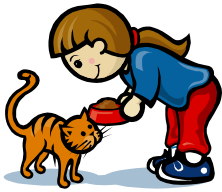
We know that you have arthritis

We want to learn why you have arthritis.

We want to find out how your arthritis affects you.

We will get this information from the doctors and nurses you see for your arthritis appointments

You may need to give a small sample of your blood which will feel like a pin prick, but this will be taken during your normal hospital visit

IF YOU HAVE ANY QUESTIONS YOU CAN ASK YOUR MUM, DAD OR ONE OF THE PEOPLE TAKING CARE OF YOU AT THE HOSPITAL.
THANK YOU FOR READING THIS!

# Childhood Arthritis Prospective Study

## Information for children (guide age: 6-10)

Version 2, 11/05/2015

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**We would like to ask you to take part in a research study. Before you decide, it is important for you to understand what the study is about, and what will happen to you if you take part. Please read this leaflet carefully and ask us about anything that you do not understand.**

## What is the study for?

Arthritis affects about one in a thousand children. We often do not know what has caused it. In some children arthritis may go away after some months or years or may persist even when grown up. At the moment it is difficult to say how your arthritis will affect you. The aim of the study is to find those things that may help predict how you will do over the long-term. Better understanding of the course of the illness will help in choosing the best treatment for children in the future.

## Why have I been chosen?

You have been chosen because you have recently developed arthritis. You may have noticed that the joints are swollen or that they may feel painful or stiff.

## What information will we collect from you?

✪The study will collect information about you, your arthritis, medical treatment and tests, how well you are and how you grow. Some of this information will come from the team you see for your normal hospital visits and some forms will be posted to you and your family. This type of study is called an 'observational study' which means that we simply watch what happens to you -the study does not affect the treatment that you get from your doctor.

✪ You will also meet a nurse who will ask you and your family some further questions about you and your arthritis.

✪We will also keep a very small amount of your blood to be looked at in our laboratories at the University of Manchester. We will get this when you have normal tests during your hospital visits, and if you cannot do this we will take a sample of your saliva (spit).

✪We may contact you through your doctor in the future as a follow-up to this study.

✪We may ask you about other research studies that you might be interested in through your doctor.

### Do I have to take part?

✪You do not have to take part if you do not want to.

✪If you decide not to take part it will not affect how your doctors treat you.

✪ If you **do** decide to take part, and your parents agree, you can sign a form to show this if you would like to.

✪You can change your mind at any time without saying why.

The information that we would collect about you will be kept secret and stored on a computer. We will keep your name locked in the study office to help check information.

The results of the research will be written about in a medical journal, but not for a few years. Your doctor will be able to tell you about how the research is going, and nobody outside the research team will know that your information is included in the study.

If you have any questions at all you can ask one of the people looking after you, or contact::

**Dr Wendy Thomson at The University of Manchester:**
**0161 275 5037**
**wendy.thomson@manchester.ac.uk**
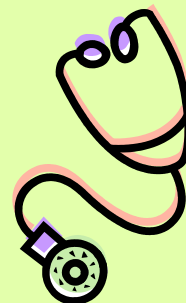
The research is funded by the **Arthritis Research UK** and is based at The University of Manchester

**Thank you for reading this information leaflet. If you do decide to take part in the study, you will be given a copy of this leaflet to keep.**

# Childhood Arthritis Prospective Study (CAPS)

**YOUNG PERSON INFORMATION SHEET** (Guide age 11-16)

Version 2, 2015-05-11, England

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**Title of Project**: Childhood Arthritis Prospective Study
**Name of Main Researcher**: Prof Wendy Thomson

✪ We would like you to take part in a research study.
✪ Please take time to read this leaflet carefully and discuss it with others if you wish.
✪ Ask us if anything is unclear, or if you would like more information.
✪ Take time to decide if you wish to take part.
**Thanks for reading this!**

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### What is the purpose of this study?

Arthritis affects about one in a thousand children. In the majority of cases we do not know what has caused it. It could be related to your genes or to the environment. The arthritis may go away after some months or years or may persist into adult life. At the moment we cannot tell who will recover and who will have more long-term problems. The aim of the study is to identify factors that may be involved in the development of arthritis and to identify factors that may help predict how you will do over the long-term. Better understanding of the course of the illness will help in choosing the best treatment for children in the future.

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### Why have you been chosen?

You have been chosen because you have recently developed an illness called arthritis.

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### Do I have to take part?

✪You do not have to take part if you do not want to.

✪If you decide not to take part it will not affect how your doctors treat you.

✪If you **do** decide to take part, and your parents agree, you can sign a form to show this if you would like to.

✪You can change your mind at any time without saying why

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### What information will we collect from you?

✪The study will collect information about you, your arthritis, medical treatment and tests, how well you are and how you grow. You will also meet a study nurse who will ask you some more questions about your arthritis. They may also ask you to complete some questionnaires. This type of study is called an 'observational study' which means that we simply watch what happens to people - the study does not affect the treatment that you get from your doctor. We will collect this data for at least the next 10 years but maybe longer.

✪ We will ask you to provide a small blood sample, which will be taken at a time when blood is also needed for routine purposes during a regular hospital visit. If you do not need a blood sample for routine clinical purposes, you will be asked to provide a saliva sample (we will get you to spit into a small cup).

- ✪ We may contact you through your doctors about other studies you may be interested in, or regarding a later follow-up of this study.
- ✪ We would want to flag you with the NHS Health and Social Care Information Centre (or their equivalent), which will provide the study with information about your health status.
- ✪ We would want to link hospital information about you with information we collect.

**Why are you taking my blood, and what will you do with the sample?**

- ✪ The research blood or saliva sample will be sent to the Centre for Musculoskeletal Research laboratories at the University of Manchester, where the **DNA** will be extracted. The exact genes to be studied cannot be identified now but will include ones we already know are important in childhood arthritis and ones discovered during the time the study is being undertaken. Some of the blood and saliva samples may be provided to other bona-fide researchers working in the field for future research of Juvenile Idiopathic Arthritis. You can refuse permission for this if you want and you can still take part in the study. No identifiable data would be stored directly with the sample, and the sample will be stored under secure conditions.

**What is genetics?**

- ✪ Genetics is the study of genes. DNA is a molecule contained within nearly all your body's cells and it contains genes within it. It is our genes that help determine certain characteristics, such as hair colour and gender as well as the likelihood that we will develop certain diseases. Genes vary between people and one of the purposes of this study is to investigate whether variation in genes determines how your arthritis affects you.

**Are there any risks to me if I take part?**

The study will run alongside your routine arthritis care; it will not influence this process. Therefore, there are no foreseeable risks associated with this study. There should be no extra risk or additional discomfort when the blood sample is taken for the study, as this will be taken at a time when blood is also needed for routine purposes during a regular hospital visit.

**What are the possible benefits of taking part?**

Although there is no clinical benefit gained by participation in the research, the information obtained from this study may result in changes in future care of patients with JIA.

**What will happen to the results of this study?**

The results of the study will be presented at scientific meetings and published in medical journals but no identifying information will be used.

**Will anyone know I have been involved with this research?**

All information used in the study is kept under secure conditions and is strictly confidential. Your GP will be informed that you are in the study.

**The research is funded by the Arthritis Research UK and is based at the University of Manchester. If you want to ask about anything please get in touch with Prof Wendy Thomson at wendy.thomson@manchester.ac.uk or on 01612755037**

**Thanks for reading this information leaflet. If you do decide to take part in the study, you will be given a copy of this leaflet to keep and will be asked to sign a consent form.**

**Study Number:** ⬚⬚⬚⬚⬚⬚

**Centre Name:** ⬚

# CONSENT FORM FOR PARENTS OR GUARDIANS OF CHILDREN TAKING PART IN RESEARCH STUDIES
## (Version 5 May 2015)

**Title of Project: Childhood Arthritis Prospective Study (CAPS)**

**Please initial box**

Name of Researcher

1. I confirm that I have read and understand the information sheet dated............ (version............) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my child's participation is voluntary and that I am free to withdraw them at any time, without giving any reason, without my child's medical care or legal rights being affected. ☐

3. I authorise the collection of information (data) from my child's medical notes for the purpose of the research study. ☐

4. I agree that I/my child can complete questionnaires about their arthritis for the purpose of the research study ☐

5. I understand that personal data and sections of my child's medical notes may be looked at by responsible people from the research team, individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my child's participation in this research. I give permission for these individuals to have access to my child's records. ☐

6. I agree that my child can provide the following samples. I understand that the collected samples, which are gifted to the Centre for Musculoskeletal Research, will be used to extract materials e.g. cells/DNA/RNA/plasma for genetic studies. I understand that the nature of the research is to study patterns of genes in large numbers of individuals and that no results on my child's genes will be fed back to me, my child's doctor or anyone else. ☐

    a)    Blood sample ☐

    b)    Spit pot ☐

    c)    If my child has a joint injection, any excess joint fluid removed ☐

7. I agree that the samples can be retained at the end of the study as coded samples. ☐

8. I agree to my child being flagged with the Health and Social Care Information Centre (HSCIC). I understand that information held and managed by The Health and Social Care Information Centre and other central UK NHS bodies may be used in order to help contact me or provide information about my child's health status.

9. I authorise the NHS Health and Social Care Information Centre or their equivalent to disclose to the CAPS research team routine health data concerning my child's hospital admissions, diagnosis and treatments. I authorise this information to be linked to the information held about my child for the purpose of the CAPS research study, even after incapacity or death.

10. I authorise research findings and datasets containing information about my child to be made available to other researchers providing that they are anonymised and that my child cannot be identified.

11. I agree that the consultant will inform my GP about my child's participation in the study.

12. I agree to my child taking part in the above study.

13. I agree to information, from which my child may be identified, being held by the research team at the Manchester University Medical School together with data collected during the study.

14. I agree that the researchers may contact me with information about other studies.

_____          _____          _____
Name of Patient                      Date                         Signature


_____          _____          _____
Name of Parent/Guardian              Date                         Signature


_____          _____          _____
Name of Person taking consent        Date                         Signature
(if different from researcher)


_____          _____          _____
Researcher                           Date                         Signature


Original copy of consent form retained by centre in site file, with 1 copy to parent/child and 1 copy to University of Manchester CAPS co-ordinating centre

**Study Number:** ☐☐☐☐☐☐

**Centre Name:** ☐

# ASSENT FORM FOR CHILDREN TAKING PART IN THE CAPS STUDY

**Title of Project: Childhood Arthritis Prospective Study (CAPS)**

Name of Researcher:

**Please initial box**

1. I have read and understand the information sheet dated .......................... (version ......)  ☐

2. I have asked all the questions that I want to ask.  ☐

3. I understand that I do not have to take part in the study and that I can stop taking part at any time without saying why.  ☐

4. I agree to people doing research collecting information from my medical notes.  ☐

5. I agree to fill out forms about my arthritis.  ☐

6. I understand that parts of my medical notes may be looked at by people doing research.  ☐

7. I understand that a small amount of my blood may be used for research.  ☐

8. I understand that a small amount of my spit may be used for research.  ☐

9. I understand that a small amount of fluid from my joint may be used for research, but only if being taken for another reason.  ☐

10. I agree to researchers linking information from the study with information collected about any hospital trips, treatment and other medical information about me.  ☐

11. I agree to information about me being shared by people doing research as long as they are not able to tell who I am from it.  ☐

12. I agree to take part in the study.  ☐

13. I agree to be contacted for future research studies.  ☐

**CAPS Children's Assent Form Version 4, 2015-05-11**
**Original copy to be filed in site file**
**1 copy for patient; 1 copy sent to co-ordinating centre;**

_____  \_\_\_\_\_  _____  _____

Name of Patient                          Age        Date                      Signature


_____  _____  _____

Name of Person taking assent             Date                      Signature
(if different from researcher)


_____  _____  _____

Researcher                               Date                      Signature

**CAPS Children's Assent Form Version 4, 2015-05-11**
**Original copy to be filed in site file**
**1 copy for patient; 1 copy sent to co-ordinating centre;**

# CAPS
# Childhood Arthritis Prospective Study

## Baseline Medical Case Notes Form

**Study ID**

**Baseline Date**

D D   M M   Y Y   Y Y

**Section A: Demographic Details of the Child**

First Name: _____

Surname: _____

Gender:     Male ☐     Female ☐

Date of Birth:
|DD|MM|Y Y|Y Y|
|☐☐|☐☐|☐☐☐☐|

Address: _____

_____

_____

_____

Postcode: ☐☐☐☐  ☐☐☐

Telephone Numbers:

Home: _____

Work _____

Mobile _____

Centre: _____

Study Number: ☐☐☐☐☐☐☐

Hospital Registration Number:

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

NHS/CHI Number:

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

## Section B: First Visit to Paediatric Rheumatologist

**DD MM Y Y Y Y**

Date of First Visit: ☐☐ ☐☐ ☐☐☐☐

What Diagnosis did the paediatric rheumatologist make?

☐

ILAR Code: ☐

Date of Recorded Symptom onset:

**DD MM Y Y Y Y**

☐☐ ☐☐ ☐☐☐☐

Source of referral to paediatric rheumatologist

GP ☐

A and E ☐

Orthopaedic Surgeon ☐

Paediatrician ☐

Physiotherapist ☐

Other ☐

If other, please specify ☐

**DD MM Y Y Y Y**

Date of Referral: ☐☐ ☐☐ ☐☐☐☐

What diagnosis did the referring doctor make?

☐

## Section C: Investigation Results

Please record ANA/CRP/ESR/FBC/Ferritin/HLA-B27 and RF test results from symptom onset up to and including baseline date (where available)

| Test Name | Date of tests | Results | Normal Ranges |
|-----------|---------------|---------|---------------|
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |
|           |               |         |               |

**Please record the following classification/disease features:**

| | Y/N/DK | Date of episode (if known) |
|---|---|---|
| | | **DD MM Y Y Y Y** |
| Fever | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Does this meet the definition of systemic JIA fever (i.e. daily for ≥ 2weeks and documented as quotidian for ≥ 3 days). | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Rash | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Did the physician record an evanescent (non-fixed) erythematous rash or systemic rash? | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Generalised lymph node enlargement | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Hepatomegaly and/or splenomegaly | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Serositis | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Psoriasis | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Family history of psoriasis in at least one 1st degree relative | ☐ | ☐☐ ☐☐ ☐☐☐☐ |

Baseline Medical Case Notes V.4 March 2010

**Classification/disease features continued:**

|  | Y/N/DK | Date of episode (if known) |
|---|---|---|
|  |  | **DD** **MM** **Y Y** **Y Y** |
| Nail abnormalities (Pitting or onycholysis) | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Dactylitis | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Enthesitis | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Sacroiliac tenderness and/or inflammatory spinal pain | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Radiological sacroiliitis | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Family history of HLA-B27 associated disease in ≥1 second degree relative | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| Presence of anterior uveitis (acute or chronic) | ☐ | ☐☐ ☐☐ ☐☐☐☐ |
| History of macrophage activation syndrome | ☐ | ☐☐ ☐☐ ☐☐☐☐ |

Baseline Medical Case Notes V.4 March 2010

Record of any imaging studies (X-rays, MRI, Ultrasound Scan, Bone Scan and DEXA)
(Please send copies of the test results)

| Joint/Region | Image Type | Date | | | | | | | | | | Result |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D | D | - | M | M | - | Y | Y | Y | Y | |
| | | | | | | | | | | | | |

**On the first visit, what treatment for JIA did the paediatric rheumatologist recommend?**
**(Please tick all that apply)**

| | | |
|---|---|---|
| Ophthalmologist | ☐ | If yes to Ophthalmology, was that in this hospital ☐ |
| Referral to nurse specialist | ☐ | Or another hospital ☐ |
| Physio | ☐ | Hospital name/s |
| Joint injection | ☐ | |
| Admission | ☐ | |
| Splinting | ☐ | |
| Orthotics | ☐ | |
| Podiatry | ☐ | |
| Surgery | ☐ | |
| Other | ☐ | |

If OTHER, please specify

**Drug History**

Prescribed/recommended DMARD/biologic medication up until date of first visit and prescribed/recommended medication at first visit to paediatric rheumatologist

**If the patient has been prescribed MTX/Biologic or DMARD, please consider completing the MTX form at this time.**

| Drug | Trade Name | Date Started | | | | | | | | | | | Date Stopped | | | | | | | | | | | Route | Stop Reason | Type of Reaction | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D | D | - | M | M | - | Y | Y | Y | Y | | D | D | - | M | M | - | Y | Y | Y | Y | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | - | | | - | | | | | | | | - | | | - | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |

## Medication key/instructions

**DMARD/ Biologics**

Adalimumab/Humira  Hydroxychloroquine
Anakinra/Kineret  Infliximab/Remicade
Azathioprine  Leflunomide
Chloroquine  Methotrexate (MTX)
Cyclophosphamide  Rituximab/Mabthera
Cyclosporine  Sulphasalazine (SSZ)
Etanercept/Enbrel  Tocilizumab/Roactmera

**Code for reason for stopping**
1. Adverse reaction. a) skin, b) blood, c) gut, d) renal, e) other
2. Inefficacy  3. Disease remission
4. Planned course complete  5. Lack of adherence
6. Other  7. Still taking drug
  9. Serious infection

Has the patient received any oral steroids <u>since symptom onset</u>?

Yes ☐          No ☐          DK ☐

Is the patient <u>currently</u> taking oral steroids?

Yes ☐          No ☐          DK ☐

Has patient received any IV steroids <u>since symptom onset</u>?

Yes ☐          No ☐          DK ☐

Is the patient currently receiving IV steroids?

Yes ☐          No ☐          DK ☐

Has the patient received any NSAIDs <u>since symptom onset</u>?

Yes ☐          No ☐          DK ☐

Is the patient <u>currently</u> taking NSAIDs?

Yes Daily ☐     Yes, as required ☐     No ☐     DK ☐

Is the patient <u>currently</u> receiving any topical eye treatment?

Yes ☐          No ☐          DK ☐

If yes, what type of treatment?

Mydriatic ☐     Steroid ☐     Anti-inflammatory ☐

Has the patient received any intra-articular steroid injections prior to, or on the day, of the first rheumatology visit? (Please record each injection separately, continue on additional sheet if required)

Yes ☐          No ☐          DK ☐

If yes, date:     **DD** ☐☐   **MM** ☐☐   **Y Y   Y Y** ☐☐☐☐

If yes which joint/s? ☐

Is the patient currently taking topical treatment for psoriasis?

Yes ☐          No ☐          DK ☐

Height at first paediatric rheumatology visit:

☐☐☐ . ☐☐ cm

Not known ☐

Date: **DD** ☐☐ **MM** ☐☐ **Y Y   Y Y** ☐☐☐☐

Weight at first paediatric rheumatology visit:

☐☐☐ . ☐☐ Kg

Not known ☐

Date: **DD** ☐☐ **MM** ☐☐ **Y Y   Y Y** ☐☐☐☐

### Section D: Your details

Today's date      **DD** ☐☐ **MM** ☐☐ **Y Y   Y Y** ☐☐☐☐

Nurse's initials      ☐☐☐☐

Nurse's signature      ☐

# CAPS
# Childhood Arthritis Prospective Study

## Nurse's Baseline Form

**Study ID**

**Baseline Date**

D D  M M  Y Y  Y Y

**Section A: Demographic Details of the Child**

Study Number: ☐☐☐☐☐☐☐

First Name: ☐

Surname: ☐

Centre: ☐

Gender:     Male ☐     Female ☐

Country of birth

Date of Birth:   DD ☐☐   MM ☐☐   Y Y ☐☐   Y Y ☐☐

☐

Home Address: ☐

Postcode: ☐☐☐☐  ☐☐☐

Telephone Numbers

Home: ☐

Are you happy to be contacted by telephone?

Yes ☐     No ☐

Work: ☐

Mobile: ☐

Are you happy to be contacted by e-mail?

Yes ☐     No ☐

Email Address: ☐

Nurse's Baseline Form V.4 March 2010

**<u>Ethnic Group</u>**

Choose ONE from sections 1 to 5, then tick the appropriate box to indicate the child's cultural background

1. White
    a. British ☐

    b. Irish ☐

    c. Any other White background ☐

2. Mixed
    a. White and Black Caribbean ☐

    b. White and Black African ☐

    c. Any other mixed background ☐

3. Asian or Asian British
    a. Indian ☐

    b. Pakistani ☐

    c. Bangladeshi ☐

    d. Any other Asian background ☐

4. Black or Black British
    a. Caribbean ☐

    b. African ☐

    c. Any other Black background ☐

5. Chinese or other ethic group
    a. Chinese ☐

    b. Any other ethnic group ☐

In the case of being "Any other ….." In categories 1 to 5, please insert details here

☐

3

## Section B: History of Arthritis

Date of onset of joint symptoms

DD MM Y Y Y Y
☐☐ ☐☐ ☐☐☐☐

Date first time symptoms were assessed by a physician

DD MM Y Y Y Y
☐☐ ☐☐ ☐☐☐☐

Where?    GP ☐    Accident & Emergency ☐

Other: ☐

What where the key concerns you had that led you to take your child to a physician for the first time?

☐

Did anyone else suggest to you that your child might need to see a physician? (tick as appropriate)

Family member ☐    School teacher ☐

Health visitor ☐    School nurse ☐

Other:    Nursery nurse ☐

☐

Before being referred to paediatric rheumatology, how many times did you have to visit …? (Give approximate numbers)

GP surgery ☐☐    Hospital day unit ☐☐☐

A&E ☐☐    Out-patient clinic ☐☐☐

Other:    In-patient ward ☐☐☐

☐

And how many __different__ practitioners did you child see before paediatric rheumatology? (Give approximate numbers)

GPs ☐☐    Orthopaedic surgeons ☐☐☐

Other:    Paediatricians ☐☐☐

☐

Did your child have any of the following before the first assessment by paediatric rheumatology?

MRI of joint(s) ☐    Arthroscopy of joint ☐

## Section C: Family History

Please list other people living in the same household

| | Relationship to child | Age (if <18) |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

How many siblings does the child have?

Full    Half

☐☐    ☐☐

What is the child's position in the family?
e.g. 3 out of 7 children (including all siblings)

☐☐ out of ☐☐

Please give details of <u>any</u>:

| | First degree relatives (Parents, siblings) | Second degree relatives (Grandparents, uncles, aunts) |
|---|---|---|
| Arthritis Specify (osteo, inflammatory, unknown) | | |

If inflammatory please indicate in each case if:

**Rheumatoid Arthritis** ☐  **Psoriatic Arthritis** ☐  **Ankylosing Spondylitis** ☐  **Reactive or Reiters** ☐  **Juvenile** ☐  **Other** ☐  **Specify:** _____

| | First degree relatives | Second degree relatives |
|---|---|---|
| Psoriasis | | |
| Diabetes Specify (IDDM, non-IDDM) | | |
| Over or underactive thyroid | | |
| Inflammatory Bowel Disease (i.e. Crohn's disease or ulcerative colitis) | | |
| Other auto-immune disease | | |
| Uveitis (indicate if acute, chronic or if type not known) | | |

**Section D: Previous medical history of child**

Duration of Pregnancy

37-40 weeks ☐

Less than 37 weeks ☐

Greater than 40 weeks ☐

Not Known ☐

|  | Yes | No |
|---|---|---|
| Pregnancy complications | ☐ | ☐ |
| Neonatal complications | ☐ | ☐ |

If complications, please provide details

☐

|  | Yes | No |
|---|---|---|
| Singleton pregnancy | ☐ | ☐ |
| Was the child breastfed? | ☐ | ☐ |

If breastfed, for how long? ☐☐ weeks

Is the child:

Right handed ☐    Ambidextrous ☐

Left handed ☐    Don't know ☐

Immunisation History

|  | Yes | No | Don't know |
|---|---|---|---|
| Are all immunisations up to date? | ☐ | ☐ | ☐ |
| Did your child have any immunisations in the 2 months prior to onset of joint symptoms? | ☐ | ☐ | ☐ |

If yes, what immunisations?

☐

Birth weight:

☐☐ lb ☐ oz    Not known ☐

☐☐ . ☐ kg

Birth length:

☐☐☐ cm    Not known ☐

**Past medical illnesses (tick as appropriate)**

Congenital problems:    Y/N/DK

Talipes/Club foot    ☐

Developmental or
Congenital dysplasia hip    ☐

Other    ☐

☐

Genetic problems:    Y/N/DK

Down's Syndrome    ☐

22qll (di George)    ☐

Other    ☐

Details: ☐

Chronic health problems:    Y/N/DK

Allergies    ☐

Asthma    ☐

Diabetes Mellitus    ☐

Eczema    ☐

Allergic Rhinitis    ☐

Crohn's Disease/
Ulcerative Colitis    ☐

Psoriasis    ☐

Uveitis    ☐

If yes to Uveitis, has this
affected the child's vision?    ☐

Other    ☐

Details: ☐

Childhood infections    Y/N/DK

Chicken Pox    ☐ Age ☐☐ Years

Measles    ☐ Age ☐☐ Years

Mumps    ☐ Age ☐☐ Years

Rubella    ☐ Age ☐☐ Years

For girls 10 or older: have they started to menstruate?   Yes ☐   No ☐

If yes, date of first period:   **DD** ☐☐  **MM** ☐☐  **Y Y Y Y** ☐☐☐☐

Mother's age at first menstruation?   ☐☐ Years

**Present Treatment**

| | Y/N/DK | | Y/N/DK |
|---|---|---|---|
| **NSAID/Anti-Inflammatory** | ☐ | **Biologic** | ☐ |
| **Steroids** | ☐ | (tick as appropriate) | |
| **DMARD** | ☐ | Adalimumab/Humira | ☐ |
| (tick as appropriate) | | Anakinra/Kineret | ☐ |
| Azathioprine | ☐ | Etanercept/Enbrel | ☐ |
| Chloroquine | ☐ | Infliximab/Remicade | ☐ |
| Cyclophosphamide | ☐ | Rituximab/Mabthera | ☐ |
| Cyclosporine | ☐ | Tocilizumab/Roactmera | ☐ |
| Hydroxychloroquine | ☐ | Other | ☐ |
| Leflunomide | ☐ | | |
| Methotrexate | ☐ | Please specify_____ | |
| Sulphasalazine | ☐ | | |
| Other | ☐ | | |

Please specify_____

**Eye drops or topical eye treatment** ☐

## Section E: Family demographics

For all parents and guardians living in the house,

For income please refer to the coding beneath. Please only complete income for those in full time employment

| | | | |
|---|---|---|---|
| Name: | | | |
| Occupation: | | | |
| Income (at time of onset): | ☐ | ☐ | ☐ |
| Age left full time education: | ☐ | ☐ | ☐ |
| Completed 6th form (Y/N/DK): | ☐ | ☐ | ☐ |
| Attended college/university (Y/N/DK): | ☐ | ☐ | ☐ |
| Has a degree (Y/N/DK): | ☐ | ☐ | ☐ |

## Income coding

| Income | Code |
|---|---|
| < £10 000 | 1 |
| £10 000-£14 999 | 2 |
| £15 000-£19 999 | 3 |
| £20 000-£24 999 | 4 |
| £25 000-£29 999 | 5 |
| £30 000-£34 999 | 6 |
| £35 000-£39 999 | 7 |
| > £40 000 | 8 |
| Missing | 9 |

Nurse's Baseline Form V.4 March 2010

GP Details

Name ☐

Address ☐

☐

☐

☐

Hospital ☐

Rheumatologist ☐

## Section G: Nurse's Details

|  | DD | MM | Y Y  Y Y |
|---|---|---|---|

Today's date ☐☐ ☐☐ ☐☐☐☐

Nurse's initials ☐☐☐☐

Nurse's signature ☐

Who provided most of the information on this questionnaire?

☐

What is his/her relationship to the child?

☐

**I you think this family are unable to complete the other forms (CHAQ, CHQ, MFQ, IPQ & GHQ) due to language difficulties, please tick.** ☐

| Centre: | Study No: | Visit No: | Completed by (please tick):<br>Mother/Father/Other – If other please give details<br>including gender: |
|---------|-----------|-----------|---------------------------------------------------------------------------------------------------------|

## CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE
1990 © Original version Singh G et al. 1998 © Cross-cultural version Woo P, Murray P, Nugent J

### THIS FORM IS FOR PARENTS TO COMPLETE

**We are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please tick the <u>one</u> response which best describes his/her usual activities <u>OVER THE PAST WEEK</u>. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS. If most children at your child's age are not expected to do a certain activity, please mark it as 'not applicable'. For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young, but not because he/she is RESTRICTED BY ILLNESS, please mark it as 'not applicable'.**

*At the end, please go back and check once again that every item has been answered.*

|  | Without ANY Difficulty | With SOME difficulty | With MUCH difficulty | UNABLE to do | Not applicable |
|---|:---:|:---:|:---:|:---:|:---:|
| **DRESSING & PERSONAL CARE** | | | | | |
| Is your child able to: | | | | | |
| - Dress, including tying shoelaces and doing buttons? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Shampoo his/her hair? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Remove socks? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Cut fingernails? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **GETTING UP** | | | | | |
| Is your child able to: | | | | | |
| - stand up from a low chair or floor? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Get in and out of bed ? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **EATING** | | | | | |
| Is your child able to: | | | | | |
| - Cut his/her own meat? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Lift a cup or glass to mouth? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Open a new cereal box? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **WALKING** | | | | | |
| Is your child able to | | | | | |
| - Walk outside on flat ground? | ☐ | ☐ | ☐ | ☐ | ☐ |
| - Climb up five steps? | ☐ | ☐ | ☐ | ☐ | ☐ |

**\* Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

Devices used for dressing ☐
(button hook, zip pull, long-handled shoe horn, etc.)
Walking stick ☐
Walking frame ☐          Built up pencil or special utensils ☐
Crutches ☐               Special or built up chair ☐
Wheelchair ☐            Other _____ ☐

**\* Please tick any categories for which your child usually needs help from another person BECAUSE OF PAIN OR ILLNESS:**

Dressing and personal care ☐     Eating ☐
Getting up ☐                      Walking ☐

| | Without ANY Difficulty | With SOME Difficulty | With MUCH Difficulty | UNABLE To do | Not Applicable |
|---|---|---|---|---|---|

**HYGIENE**
Is your child able to
- Wash and dry your entire body? ☐ ☐ ☐ ☐ ☐
- Take a bath (get in and get out)? ☐ ☐ ☐ ☐ ☐
- Get on and off the toilet or potty? ☐ ☐ ☐ ☐ ☐
- Brush teeth? ☐ ☐ ☐ ☐ ☐
- Comb/brush hair? ☐ ☐ ☐ ☐ ☐

**REACH**
Is your child able to:
- Reach and get down a heavy object such as a large game or books from just above his/her head? ☐ ☐ ☐ ☐ ☐
- Bend down to pick up clothing or a piece of paper from the floor? ☐ ☐ ☐ ☐ ☐
- Pull on a jumper over his/her head? ☐ ☐ ☐ ☐ ☐
- Turn neck to look back over shoulder? ☐ ☐ ☐ ☐ ☐

**GRIP**
Is your child able to:
- Write or scribble with pen or pencil? ☐ ☐ ☐ ☐ ☐
- Open car doors? ☐ ☐ ☐ ☐ ☐
- Open jars, which have been
- previously opened? ☐ ☐ ☐ ☐ ☐
Turn taps on and off? ☐ ☐ ☐ ☐ ☐
- Push open a door when you have to turn a door knob? ☐ ☐ ☐ ☐ ☐

**ACTIVITIES**
Is your child able to:
- Run errands and shop? ☐ ☐ ☐ ☐ ☐
- Get in and out of a car, toy car or school bus? ☐ ☐ ☐ ☐ ☐
- Ride bike or tricycle? ☐ ☐ ☐ ☐ ☐
- Do household chores
(eg. Wash dishes, take out rubbish, hoovering) ☐ ☐ ☐ ☐ ☐
- Run? ☐ ☐ ☐ ☐ ☐

**\* Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

Raised toilet seat ☐ Bath rail ☐
Bath seat ☐ Long-handled appliances for reach ☐
Jar opener (for jars previously opened) ☐ Long-handled appliances in bathroom ☐

**\* Please tick any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

Hygiene ☐ Gripping and opening things ☐
Reach ☐ Errands and chores ☐

**PAIN : We are also interested in learning whether or not your child has been affected by pain because of his or her illness. How much pain do you think your child has had IN THE PAST WEEK? Place a mark on the line below, to indicate the severity of the pain**

No pain 0 |————————————————————| 100 Very severe pain

**GENERAL EVALUATION: Considering all the ways that arthritis affects your child, rate how he/she is doing doing by placing a single mark on the line below.**

Very well 0 |————————————————————| 100 Very poor

**Please tell us the date on which you completed this form    Date: …………………………………………………….**

| Centre: | Study No: | Visit No: | Completed by (please tick):<br>Mother/Father/Other – If other please give details including gender: |
|---------|-----------|-----------|------------------------------------------------|

Version 3 – August 2008

**CHILD HEALTH QUESTIONNAIRE (For children five years or older)**

**Parent report**

**CHQ-PF50**

This booklet asks about your child's health and well-being.  Your individual answers will not be shared with anyone.  If you choose not to participate it will not affect the care your child receives.

Answer the questions by marking <u>one</u> of the appropriate boxes.  Certain questions may look alike, but each one is different.  Some questions ask about problems your child may not have, but it's important for us to know that too.  <u>Please answer every question</u>.  <u>There are no right or wrong answers, just choose the response that you think fits your situation best</u>.

If you are unsure how to answer a question, please give the best answer you can and make a comment in the margin.  All comments will be read, so please feel free to make as many as you wish.

<u>At the end, please go back and check once again that every item has been answered.</u>

Child Health Questionnaire CHQ-PF50

**Please tell us the date on which you completed this form    Date:** [                    ]

| SECTION 1: YOUR CHILD'S GENERAL HEALTH |
|---|

1.1 In general, would you say your child's health is:

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Excellent | Very good | Good | Fair | Poor |

| SECTION 2: YOUR CHILD'S PHYSICAL ACTIVITIES |
|---|

The following questions ask about physical activities your child might do during a day.
2.1 During the past 4 weeks has your child been limited in any of the following activities due to health problems?

| | Yes, limited a lot | Yes, limited somewhat | Yes, limited a little | No, not limited |
|---|---|---|---|---|
| a. Doing things that take a lot of energy, such as playing football or netball, running? | ☐ | ☐ | ☐ | ☐ |
| b. Doing things that take some energy such as riding a bike or roller skating? | ☐ | ☐ | ☐ | ☐ |
| c. Ability (physically) to get around the neighbourhood, playground or school? | ☐ | ☐ | ☐ | ☐ |
| d. Walking 100 metres or climbing one flight of stairs? | ☐ | ☐ | ☐ | ☐ |
| e. Bending, lifting or stooping? | ☐ | ☐ | ☐ | ☐ |
| f. Taking care of him/herself, that is, eating, drinking, dressing, bathing, or going to the toilet? | ☐ | ☐ | ☐ | ☐ |

| SECTION 3: YOUR CHILD'S EVERYDAY ACTIVITIES |
|---|

3.1 During the past 4 weeks, has your child's schoolwork or activities with friends been limited in any of the following ways due to EMOTIONAL difficulties, or problems with his/her behaviour?

| | Yes, limited a lot | Yes, limited somewhat | Yes, limited a little | No, not limited |
|---|---|---|---|---|
| a. Limited in the KIND of schoolwork or activities with friends he/she could do | ☐ | ☐ | ☐ | ☐ |
| b. Limited in the AMOUNT of time he/she could spend on schoolwork or activities with friends | ☐ | ☐ | ☐ | ☐ |
| c. Limited in PERFORMING schoolwork or activities with friends (it took extra effort) | ☐ | ☐ | ☐ | ☐ |

3.2 During the past 4 weeks, has your child's schoolwork or activities with friends been limited in any of the following ways due to problems with his/her PHYSICAL health?

| | Yes, limited a lot | Yes, limited somewhat | Yes, limited a little | No, not limited |
|---|---|---|---|---|
| a. Limited in the KIND of schoolwork or activities with friends he/she could do | ☐ | ☐ | ☐ | ☐ |
| f. Limited in the AMOUNT of time he/she could spend on schoolwork or activities with friends | ☐ | ☐ | ☐ | ☐ |

| SECTION 4: PAIN |
|---|

4.1 During the past 4 weeks how much bodily pain or discomfort has your child had?

| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|---|
| None | Very mild | Mild | Moderate | Severe | Very severe |

4.2 During the past 4 weeks, how often has your child had bodily pain or discomfort?

| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|---|
| None of the time | Once or twice | A few times | Fairly often | Very often | Every/almost every day |

Child Health Questionnaire CHQ-PF50

| SECTION 5: BEHAVIOUR |
|---|

Below is a list of items that describe children's behaviour or problems they sometimes have.
5.1 How often during the past 4 weeks did each of the following statements describe your child?

|  | Very often | Fairly often | Some-times | Almost never | Never |
|---|---|---|---|---|---|
| a. Argued a lot? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Had difficulty in concentrating or paying attention? | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Not told the truth? | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Taken things which didn't belong to them? | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. Had tantrums or a hot temper? | ☐ | ☐ | ☐ | ☐ | ☐ |

5.2 Compared to other children your child's age, in general would you say his/her behaviour is:

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Excellent | Very good | Good | Fair | Poor |

| SECTION 6: WELL-BEING |
|---|

The following are about children's moods.
6.1 During the past 4 weeks how much of the time do you think your child:

|  | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Felt like crying? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Felt lonely? | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Acted nervous? | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Acted bothered or upset? | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. Acted cheerful? | ☐ | ☐ | ☐ | ☐ | ☐ |

| SECTION 7: SELF ESTEEM |
|---|

The following ask about your child's satisfaction with self, school and others. It may be helpful if you keep in mind how other children your child's age might feel about these areas.
7.1 During the past 4 weeks how satisfied do you think your child has felt about:

|  | Very satisfied | Somewhat satisfied | Neither satisfied nor dissatisfied | Somewhat dissatisfied | Very dissatisfied |
|---|---|---|---|---|---|
| a. His/her school ability? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. His/her athletic ability? | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. His/her friendships? | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. His/her looks/appearance? | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. His/her family relationships? | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. His/her life overall? | ☐ | ☐ | ☐ | ☐ | ☐ |

# Child Health Questionnaire CHQ-PF50

The following statements are about health in general.
8.1 How true or false is each of these statements for your child?

| | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
| --- | --- | --- | --- | --- | --- |
| a. My child seems to be less healthy than other children I know | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. My child has never been seriously ill | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. When there is something going around my child usually catches | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. I expect my child will have a very healthy life | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. I worry more about my child's health than other people worry about their children's health | ☐ | ☐ | ☐ | ☐ | ☐ |

8.2 Compared to one year ago, how would you rate your child's health now?

| ☐ | ☐ | ☐ | ☐ | ☐ |
| --- | --- | --- | --- | --- |
| Much better now than one year ago | Somewhat better now than one year ago | About the same now as one year ago | Somewhat worst now than one year ago | Much worse now than one year ago |

**SECTION 9: YOU AND YOUR FAMILY**

9.1 During the past 4 weeks how MUCH emotional worry or concern did each of the following cause YOU?

| | None at all | A little bit | Some-what | A lot | A great deal |
| --- | --- | --- | --- | --- | --- |
| a. Your child's physical health? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Your child's emotional well-being or behaviour | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Your child's attention or learning difficulties? | ☐ | ☐ | ☐ | ☐ | ☐ |

9.2 During the past 4 weeks were you LIMITED in the amount of time YOU had for your own needs because of:

| | Yes, limited a lot | Yes, limited somewhat | Yes, limited a little | No, not limited |
| --- | --- | --- | --- | --- |
| a. Your child's physical health? | ☐ | ☐ | ☐ | ☐ |
| b. Your child's emotional well-being or behaviour | ☐ | ☐ | ☐ | ☐ |
| c. Your child's attention or learning difficulties? | ☐ | ☐ | ☐ | ☐ |

9.3 During the past 4 weeks how often has your child's health or behaviour:

| | Very often | Fairly often | Some-times | Almost never | Never |
| --- | --- | --- | --- | --- | --- |
| a. Limited the types of activities you could do as a family? | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. Limited various everyday family activities (eating meals, watching TV)? | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. Limited your ability as a family to 'get up and go' on a moment's notice? | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. Caused tension or conflict in your home? | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. Been a source of disagreements or arguments in your family? | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. Caused you to cancel or change plans (personal or work) at the last minute? | ☐ | ☐ | ☐ | ☐ | ☐ |

9.4 Sometimes families may have difficulty in getting along with one another. They do not always agree and they may get angry. In general, how would you rate your family's ability to get along with one another?

| ☐ | ☐ | ☐ | ☐ | ☐ |
| --- | --- | --- | --- | --- |
| Excellent | Very good | Good | Fair | Poor |