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## OBSERVATIONAL STUDY OF PEDIATRIC RHEUMATIC DISEASES: THE CARRA REGISTRY

**Date:** August 7, 2014

**Version:** 1.0

**Study Sponsor:** CARRA

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**PROTOCOL APPROVALS**

**Study Title:** Observational Study for Pediatric Rheumatic Diseases: The CARRA Registry  
**Version:** Protocol Version 1.0  
**Date of Issue:** August 7, 2014  
**Study Sponsor:** CARRA

We, the undersigned, have read and approve this protocol and agree on its content.



On behalf of CARRA  
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Date

12/15/14



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Date

12/13/14

## INVESTIGATOR AGREEMENT

I have read the CARRA Registry protocol Version 1.0, including all appendices and I agree that it contains all necessary details for my staff and I to conduct this protocol as described. I will personally oversee protocol conduct as outlined herein.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the CARRA Registry Clinical and Data Coordinating Center (CDCC). I will discuss this material with personnel to ensure that they are fully informed about the conduct of the protocol and the information being collected from patients enrolled in the CARRA Registry. I am aware that, before commencement of this study at my clinical facility, the local institutional review board must approve this protocol. I agree to make all reasonable efforts to adhere to the CARRA Registry protocol.

I, or my designee, agree to be present at all site visits and investigator meetings. In addition, I will ensure the presence of relevant study personnel under my supervision at these visits and meetings.

I agree to provide all subjects with a signed copy of the informed consent form, as required by government and International Conference on Harmonization regulations. I further agree to report to the CDCC any protocol deviations in accordance with the terms of this protocol, Good Clinical Practice Guidelines and applicable regulatory requirements. All information pertaining to the protocol shall be treated in a confidential manner.

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Principal Investigator Name (print)

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Signature

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Date

## PROTOCOL VERSION AND AMENDMENT TRACKING

Version No.	Date
Protocol Version 1.0	August 4, 2014

## PROTOCOL SYNOPSIS

<b>Protocol Number</b>	Version 1.0
<b>Protocol Title</b>	Observational Study of Pediatric Rheumatic Diseases: The CARRA Registry
<b>Sponsor</b>	CARRA
<b>Product</b>	Registry
<b>Diagnosis and Main Criteria for Inclusion</b>	<ol style="list-style-type: none"> <li>1. Onset of rheumatic disease prior to age 16 years for juvenile idiopathic arthritis and onset prior to age 19 years for all other rheumatic diseases</li> <li>2. Subject and/or parent/legal guardian is able to provide written informed consent and willing to comply with study procedures.</li> <li>3. Subject and/or parent/ legal guardian can read either English or Spanish.</li> <li>4. Subject and/or parent/ legal guardian is willing to be contacted in the future by study staff.</li> </ol>
<b>Main Criterion for Exclusion</b>	Greater than 21 years of age at the time of enrollment.
<b>Primary Study Objectives</b>	<ol style="list-style-type: none"> <li>1. Prospectively collect essential data from children, adolescents and young adults with pediatric onset rheumatic diseases.</li> <li>2. Evaluate the safety of therapeutic agents in persons with pediatric onset rheumatic diseases.</li> </ol>
<b>Secondary Study Objective</b>	<ol style="list-style-type: none"> <li>1. Evaluate clinical outcomes associated with the use of therapeutic agents in persons with pediatric onset rheumatic diseases.</li> <li>2. Document drug treatment patterns and clinical course of persons with pediatric-onset rheumatic diseases over time.</li> <li>3. Evaluate factors other than drug treatment that are associated with clinical outcomes in pediatric onset rheumatic diseases.</li> </ol>
<b>Study Procedures</b>	<ol style="list-style-type: none"> <li>1. Obtain consent from subject and/or parent/ legal guardian.</li> <li>2. Collect baseline and follow-up data on subjects' demographics, quality of life, general, and disease-specific health including medication use, serious adverse events, adverse events and events of special interest.</li> <li>3. Enter baseline and follow-up data into an electronic data entry system via direct data entry and/or electronic medical record data download.</li> </ol>
<b>Treatment Regimen(s)</b>	None. Patients will receive diagnostic and therapeutic interventions per standard of care.

<b>Duration/End-of-Study Definition</b>	This study will continue as long as the Registry remains in existence with a goal of 10 years of follow-up for each subject. The long-term follow-up program may allow for data collection beyond 10 years of follow-up.
<b>Number of Subjects</b>	Eligible subjects will be enrolled at CARRA Registry sites with no maximum number of subjects.
<b>Number of Sites</b>	No fewer than 50 participating clinical sites in North America (as well as additional international sites). The lead investigator at each participating clinical site will be a CARRA member in good standing.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ACR	American College of Rheumatologists
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CDCC	Clinical and Data Coordinating Center
CFR	Code of Federal Regulations
CSS	Churg Strauss Syndrome
DCRI	Duke Clinical Research Institute
DOB	Date of Birth
DMARD	Disease-modifying antirheumatic drug
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDSS	Enhanced Drug Safety Surveillance
EHR	Electronic Health Record
ESI	Event of Special Interest
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
i2b2	Informatics for Integrating Biology and the Bedside
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JDM	Juvenile Dermatomyositis
JIA	Juvenile Idiopathic Arthritis
JDM	Juvenile Dermatomyositis
MCTD	Mixed Connective Tissue Disease
NIH	National Institutes of Health
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifying Information
PRO	Patient-Reported Outcome
RF	Rheumatoid Factor
SAE	Serious Adverse Event
sJIA	Systemic Juvenile Idiopathic Arthritis
SLE	Systemic Lupus Erythematosus
SSN	Social Security Number
TNF	Tumor Necrosis Factor
US	United States

## 1 EXECUTIVE SUMMARY

The original Childhood Arthritis & Rheumatology Research Alliance (CARRA) Registry (Protocol Number: CRNT\_REGST01) was first established in 2010 to advance alliance infrastructure, facilitate expanded clinical and translational pediatric research, and transform the culture of pediatric rheumatology toward universal participation in research. This original CARRA Registry will be referred to throughout this protocol as the CARRA Legacy Registry. Through the creation of a sophisticated informatics infrastructure, provision of comprehensive site support and the engagement of families, patients, and communities, the CARRA Registry will provide the opportunity for affected children at every CARRA Registry site to participate in high-quality clinical and translational research.

Continuation of the CARRA Registry as described in this protocol will support data collection on patients with pediatric-onset rheumatic diseases. The CARRA Registry will form the basis for future CARRA studies. In particular, this observational registry will be used to answer pressing questions about therapeutics used to treat pediatric rheumatic diseases, including examining safety questions. The Duke Clinical Research Institute (DCRI) is serving as the CARRA Clinical and Data Coordinating Center (CDCC) for this protocol.

Traditional exposure-based post-marketing registries of individual therapeutic agents for juvenile idiopathic arthritis (JIA), systemic lupus erythematosus, and other rheumatic diseases are inadequate for answering important safety questions for many reasons:

- Sample sizes are too small to detect uncommon but important events
- No unexposed comparators exist to evaluate risk attributable to underlying disease
- Duration of follow-up of individual patients is too short to evaluate many potential delayed adverse events (AEs)
- Sample sizes are inadequate to assess myriad complex and dynamic concurrent medication regimens common to treatment of rheumatic diseases
- Selective patient enrollment limits evaluation of co-morbid conditions and other patient factors

These limitations prevent patients, families, and providers from understanding the true risks and benefits of therapy in order to make appropriate and informed decisions. They also

prevent drug manufacturers and regulatory agencies from conducting an informed review of marketed products for these diseases.

A registry based on disease diagnosis rather than specific therapeutic agents overcomes many of the limitations of exposure-based single-agent registries in the assessment of delayed or uncommon safety events. Indeed, data from a consolidated disease-based registry “...could provide the information necessary for individual companies to satisfy post-marketing requirements and commitments and obviate the need for an individual product registry” (letters from the United States (US) Food and Drug Administration (FDA) to CARRA, 21 December 2010 and 9 December 2011). This protocol details the foundation of a registry to meet these objectives.

The CARRA Registry aims to detect and understand the epidemiology of important AEs, including those that are delayed or uncommon. Subjects followed at active CARRA Registry sites are eligible for enrollment, regardless of past or current treatment. Each subject will be followed prospectively for a goal of 10 years duration; the study will continue indefinitely as resources allow and continued need exists. Data will be systematically collected, including important patient factors, therapies, serious adverse events (SAEs), and protocol-defined events of special interest. Selected safety events (e.g., malignancies) will be adjudicated by a panel of experts via a review of medical records. The CARRA Registry, a disease-based prospective observational registry, enables both detection of potential safety signals and hypothesis-driven, rigorous, and adequately-controlled pharmacoepidemiologic studies of important AEs and their associations with therapeutic agents.

In addition to answering questions about the safety of therapeutics, the data collected in the CARRA Registry are anticipated to serve many other valuable uses. Within the confines of observational study design, the effectiveness of therapeutic agents may be examined for short- and long-term clinical and patient-centered outcomes. The Registry is the data collection platform for Consensus Treatment Plan research in pediatric rheumatic disease. Medication use for pediatric rheumatic diseases is dynamic and not well characterized. The CARRA Registry represents a powerful data source to follow drug use patterns and provides the opportunity to study predictors of medication use. Important outcomes are likely to be influenced by other factors in addition to therapy (e.g., disease severity) and the CARRA Registry is positioned to help answer these types of questions. Patient-reported outcomes (PROs) generated by patients outside the context of clinical encounters may be collected in the Registry to provide a rich,

additional dimension of data to better understand rheumatic diseases. Practitioners may review clinical data from their sites as part of a quality improvement approach to better outcomes.

Analyses of CARRA Registry data aim to provide results to guide the therapeutic decisions made by affected children, families, and providers while improving regulatory efficiency and reducing cost. Ultimately, this approach might serve as a model for successful collaboration between research community networks, industry, and public agencies to promote the effective and efficient evaluation of drugs and devices across the regulatory continuum.

## **2 BACKGROUND AND RATIONALE**

### **2.1 LONG-TERM SAFETY OF THERAPIES**

About 300,000 children in the US are affected by rheumatic diseases, which include JIA, SLE, dermatomyositis, and vasculitis. The most common of these diseases is JIA (Sacks 2007), which tends to have a chronic unrelenting course (Cassidy 2011, Singh-Grewal 2006, Lomater 2000). Most children with JIA continue to have active arthritis into adulthood (Packham 2002). In addition, children with JIA are at risk for developing significant short- and long-term disabilities (Minden 2002, Bowyer 2003).

Initial treatments for JIA included disease-modifying anti-rheumatic drugs such as methotrexate, nonsteroidal anti-inflammatory drugs, corticosteroids (oral and intra-articular), gold injections, sulfasalazine, and hydroxychloroquine. The late 1990s saw the introduction of biologic agents—tumor necrosis factor (TNF) inhibitors—that revolutionized prognosis through improved effectiveness (Hayward 2009, Lovell 2000). Since then, several biologic agents have been developed targeting various immunologic proteins important in inflammatory arthritis. Marketing approval for these agents have carried the requirement to conduct post-authorization studies (known in the US as Phase IV) studies to refine the safety profile.

However, current strategies for collecting and analyzing data regarding the long-term safety of these therapies are not only burdensome; they also may not yield robust information to manufacturers, regulators, providers or patients. As an example, in 2009 the FDA placed a “boxed warning” on TNF inhibitors for children because of a potentially increased risk of malignancy, raising many questions and concerns. However, the warning was based upon



analysis of voluntary reports of malignancies among children who had received TNF inhibitors (Diak 2010).

This case illustrates several difficulties inherent in assessing the long-term safety of individual drugs used in children with chronic disease. First, the analysis did not account for the likely underreporting of events inherent in any voluntary reporting system. The small number of patients also makes interpretation of findings difficult and the true number of exposed patients is unknown. The analysis used children in the general population as the comparator group rather than children with similar diseases who had not been exposed to TNF inhibitors. There was no adjustment for exposure to multiple agents, whether of the same or different therapeutic classes, serially or in combination throughout the disease course. Finally, the pathophysiology of the disease itself might play a role in the risk for rare AEs such as malignancy, opportunistic infections, pulmonary hypertension, and various inflammatory conditions, irrespective of therapy (Hayward 2009, Lovell 2006, Wallace 2009, [www.carragroup.org](http://www.carragroup.org), [www.carranetwork.org](http://www.carranetwork.org)), which was not accounted for in the analysis.

Regarding other agents approved for use in children with rheumatic diseases, single-product, Phase IV safety registry studies have been completed for two products thus far (etanercept and celecoxib) (Lovell 2006). Similar studies are ongoing for adalimumab and abatacept. Although analyses of these single-product registries may technically fulfill FDA requirements and manufacturers' commitments for post approval surveillance, they will suffer many of the limitations identified for the TNF inhibitor analysis. Moreover, for some agents, the approved disease indication is too rare to allow study in a Phase IV single-agent registry. Also, AEs and outcomes associated with the off-label use of many other types of agents can elude capture in existing systems.

In summary, the single-agent registry approach to post-marketing surveillance appears to yield little useful data regarding the long-term safety of agents commonly used in children with rheumatic diseases.

## 2.2 THE USE AND EFFECTIVENESS OF THERAPEUTIC AGENTS

There are many therapeutic agents currently used in the treatment of pediatric onset rheumatic diseases and it is anticipated that many more will become commercially available in the near future. Currently, the clinical response to a therapeutic agent in a particular individual patient

cannot be reliably predicted and not all patients are able to achieve the desired state of inactive disease. Therefore, the medication treatment regimens used in pediatric onset rheumatic disease are complex and dynamic and consequently poorly characterized. By collecting essential data elements, including medication use, the CARRA Registry can effectively and accurately report and follow changes in current medication use patterns. Data can also be used to investigate predictors of medication use patterns and compare use patterns to current treatment recommendations or other proposed standards.

Many therapeutic agents have demonstrated clear efficacy in randomized controlled trials of the treatment of pediatric onset rheumatic diseases. Some of these agents have been studied in longer-term studies of effectiveness (i.e., “real-world” studies) and demonstrated clear benefit. Nevertheless, there remains much to be learned about the short- and long-term clinical and patient-centered outcomes associated with therapeutics agents. The CARRA Registry will enable many studies of effectiveness, although these studies may be limited by the observational design of the Registry. By collecting essential data on baseline disease characteristics and measures of disease activity, it may be possible to control for confounding by indication and estimate the true benefit of therapeutic agents.

The Registry is the data collection platform for Consensus Treatment Plan research in pediatric rheumatic disease. These observational studies evaluate clinical outcomes resulting from the use of various currently accepted and standardized treatment approaches.

### 2.3 PATIENT FACTORS ASSOCIATED WITH DISEASE OUTCOMES

Clearly, there are factors associated with disease outcomes in addition to the use of therapeutic agents. However, for most pediatric onset rheumatic diseases, these additional factors are not well understood or sufficiently sensitive or specific to drive clinical decision making. Through the long-term systematic capture of treatments, clinical outcomes and patient-specific factors, the CARRA Registry will enable investigations to assess predictors of particular disease outcomes. Such knowledge could be applied to optimize the care of persons with pediatric onset rheumatic diseases.

## 2.4 ABOUT CARRA

CARRA is a research network of 107 pediatric rheumatology sites in the US and Canada, founded in 2002 by pediatric rheumatologists ([www.carragroup.org](http://www.carragroup.org)). Its mission is to improve the care of children with rheumatic diseases by fostering and conducting high-quality clinical and translational research.

In 2009, CARRA was awarded two American Recovery and Reinvestment Act grants from the National Institutes of Health (NIH), one funded the development and implementation of a large multicenter registry of pediatric rheumatic diseases and its informatics infrastructure (RC2 AR058934) (CARRAnet) ([www.carranetwork.org](http://www.carranetwork.org)). This grant successfully established the CARRA Registry (referred to as the CARRA Legacy Registry in this protocol) and an innovative, state-of-the-art secure informatics infrastructure using electronic data capture (EDC) for data collection and allowing data analysis using an open-source, ontology-based framework — Informatics for Integrating Biology and the Bedside (i2b2), an ideal foundation for pharmacosurveillance data collection. The funding also supported a robust training initiative for site investigators and coordinators, as well as contracting capability and central site management in the Registry's CDCC, located at DCRI. The CARRA Registry is an observational registry that collects longitudinal information on children and adolescents who have pediatric rheumatic diseases at 63 academic pediatric rheumatology centers in the US and Canada.

CARRA has already conducted a prospective safety-reporting study: the Enhanced Drug Safety Surveillance (EDSS) study (Wallace 2009). This study obtained safety data through monthly emails to CARRA physicians requesting information about the occurrence of SAEs in their patients (Wallace 2009). Although this approach was shown to be feasible, the lack of complete disease and medication information on all patients made accurate assessment of the frequency of events of special interest (ESIs) difficult and the assessment of formal causal associations impossible.

### 2.4.1 ENROLLMENT IN THE CARRA LEGACY REGISTRY

As of June 2014, CARRA sites enrolled almost 10,000 patients, 70% of whom have JIA (n=6391). The breakdown of the CARRA Registry patients' JIA categories were as follows: systemic JIA (541), RF- polyarticular JIA (1907), RF+ polyarticular JIA (435), persistent

oligoarticular JIA (1768), extended oligoarticular JIA (460), psoriatic JIA (361), enthesitis-related JIA (660), juvenile ankylosing spondylitis (35), undifferentiated JIA (157), and other JIA (67).

The breakdown for diseases other than JIA was as follows: systemic lupus erythematosus (989), juvenile dermatomyositis (631), localized scleroderma (180), mixed connective tissue disease (143), vasculitis (190), uveitis (100), fibromyalgia (180), systemic sclerosis (63), sarcoidosis (29), and sjogren syndrome (25).

These patients were enrolled as a cross-sectional convenience sample of prevalent and incident cases and irrespective of medication exposure. Biologic usage in the JIA population was as follows: 2,763 were currently or in the past been exposed to a biologic (mainly TNF, IL1, IL6, and T-cell receptor co-stimulation inhibitors), and of these 1,494 had RF-polyarticular JIA, RF+polyarticular JIA, or extended oligoarticular JIA.

## 2.5 RATIONALE

In contrast to traditional, single-product safety registries, a consolidated prospective disease-based registry addresses many of the limitations discussed. Enrolling patients into a single registry provides the following advantages:

- Allows for robust detection of SAEs, and ESIs
- Surveys AEs and outcomes, contrary to passive reporting systems
- Assesses concurrent and sequential medication use
- Provides access to appropriate comparator groups when assessing the frequency of an AE by exposure to specific agents, by disease state, or both
- Allows the medical community to follow patients over extended time periods providing improved detection and assessment of AEs with long latency periods
- Reflects clinical practices in the “real world”
- Enables the study of drug use, drug effectiveness, and the influence of patient factors on important outcomes.

The current protocol for the CARRA Registry aims to refactor the infrastructure of the legacy Registry to collect and analyze safety data in the context of the natural history of rheumatic disease in children focusing on more robust collection of medication data, SAEs, and long-term follow up.

Children with rheumatic diseases will be included regardless of current or past treatment and followed prospectively with a 10-year follow-up goal. Patients will continue to be followed in adulthood when they are no longer treated by pediatric rheumatologists. Data on all therapies and significant AEs will be collected, with selected AEs or events of special interest adjudicated and tracked.

The Registry is designed to facilitate collaboration between CARRA and multiple industry sponsors to study specific agents in the context of the natural history of the relevant disease, fulfilling post-marketing requirements and commitments. Policies for governance, scientific oversight, protocols and data analysis plans are developed in collaboration with industry sponsors, independent scientific experts, patient advocacy groups and government stakeholders. Appropriate guidelines and analysis plans are in place to manage conflicts of interest, comparisons between therapeutic agents, assessment of complex exposure histories, and responsible reporting of safety events.

Ultimately, the CARRA Registry aims to serve as a model for how research community networks can collaborate with industry and public agencies to promote more effective and efficient drug and device approvals across the regulatory continuum.

### **3 OBJECTIVES**

#### **3.1 PRIMARY OBJECTIVES:**

1. Prospectively collect essential data elements from children, adolescents and young adults with pediatric rheumatic diseases.
2. Evaluate the safety of therapeutic agents in persons with pediatric onset rheumatic diseases.

#### **3.2 SECONDARY OBJECTIVES:**

1. Evaluate clinical outcomes associated with the use of therapeutic agents in persons with pediatric onset rheumatic diseases.
2. Document drug treatment patterns and clinical course of persons with pediatric onset rheumatic diseases over time.

3. Evaluate factors other than drug treatments that are associated with clinical outcomes in pediatric onset rheumatic diseases.

## **4 BASIC STUDY DESIGN**

This is an observational cohort registry study of children with pediatric rheumatic diseases enrolled from participating CARRA sites. All patients with pediatric rheumatic diseases who are seen at a participating CARRA site for medical care will be considered for enrollment into the study. Patients are seen at baseline and then at least twice a year, and also when new biologic or non-biologic disease modifying antirheumatic drugs (DMARDs) are started. Data will be collected longitudinally from enrolled subjects (via paper or on line questionnaires, personal interview, and/or phone or electronic contact). Data may be collected from the subject's medical record or electronic health record (EHR) at any time during the subject's participation in the CARRA Registry. Data collection may also be supplemented by linkage to administrative claims data or from other sources such as regional cancer registries, the National Death Index, claims databases maintained by government and commercial insurance providers, and other external data sources (e.g., health plans and health information networks, pharmacy records, laboratory test results, other patient registries). These linkages will be performed using identifying information, such as name, DOB, address, and SSN (if provided). These data will be sufficient for the identification of safety signals and for the conduct of rigorous pharmacoepidemiologic safety studies. This protocol will be conducted in accord with the policies and procedures of the FDA guidance document: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005, and capture data in a secure manner, compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Essential data elements—including demographics, disease phenotype, disease activity, and cumulative medication exposures—will be obtained from all subjects at enrollment and approximately every 6 months as standard of care dictates during routine follow-up. Data will also be collected whenever treatment with a biologic or non-biologic DMARD is initiated. Data will continue to be collected from subjects who age out of the pediatric care setting, through a call center at the CDCC.

SAEs as defined by the FDA and protocol-defined medical events of special interest (ESIs) will be prospectively reported to the Registry by investigators at the time of the event. ESIs will be verified against medical records, such as hospital discharge summaries. Selected safety events,

such as malignancies, will be adjudicated by a panel of physicians who are content experts via review of medical records from which identifying patient information has been redacted.

Data analysis practices and procedures will be guided by the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices. Detailed analysis plans will be developed before each data analysis. Appropriate study designs will be used to estimate associations between medication exposures and SAEs and ESIs. It is anticipated that cohort study designs will be used for most analyses, but case-control, nested case-control, case-crossover, or other study designs may be appropriate to answer some questions. Comparators will be derived from subjects enrolled in the CARRA Registry who were not exposed to the medication(s) of interest. Comparators may be further defined by specific medication exposures (e.g., children who receive methotrexate) or disease state (e.g., children with polyarticular course JIA). Operational definitions of cohorts, medication exposures, confounders, etc., will be determined based on the specific study question. Confounding and effect modification will be considered in statistical models. Relevant sensitivity analyses, particularly of medication exposure risk windows, will be performed.

## **5 STUDY POPULATION**

### **5.1 INCLUSION CRITERIA**

1. Onset of rheumatic disease prior to age 16 years for JIA and onset prior to age 19 years for all other rheumatic diseases (see appendix A).
2. Subject (and/or parent/legal guardian when required) is able to provide written informed consent and willing to comply with study procedures.
3. Subject and/or parent/legal guardian can read either English or Spanish.
4. Subject and/or parent/legal guardian is willing to be contacted in the future by study staff.

### **5.2 EXCLUSION CRITERION**

1. Greater than 21 years of age at the time of enrollment.

## **6 RECRUITMENT, INFORMED CONSENT AND ENROLLMENT**

### **6.1 RECRUITMENT PROCEDURES**

CARRA Legacy Registry subjects are eligible for enrollment in this CARRA Registry protocol. Subjects will also be recruited from the patient population at CARRA Registry sites. New and established patient medical histories will be reviewed against the inclusion criteria. Potential subjects (and/or parents/legal guardians) who meet inclusion criteria will be approached at the time of a visit to the CARRA Registry site, or may be contacted prior to a regularly scheduled visit.

### **6.2 INFORMED CONSENT AND ENROLLMENT**

Subjects with pediatric-onset rheumatic diseases will be offered the opportunity to be enrolled into the CARRA Registry. If the adult subject (aged 18-21) or minor child's parent/legal guardian have read the consent/assent forms, had all questions answered to their satisfaction, and agree to participate, then written informed consent will be obtained per each enrolling site's institutional requirements. All enrolled subjects and/or their parent/legal guardian will be given a copy of the signed consent documents. Documentation regarding the informed consent process and the subject's study participation will be made in the subject's medical record and/or study source documents. Each subject for whom written informed consent is obtained and who meets all eligibility criteria will be enrolled in the CARRA Registry. At the time of enrollment, subjects and/or parent/legal guardian will be asked to provide permission for a continuing release of medical records to facilitate procurement of documentation of safety events that may occur.

### **6.3 SUBJECT NUMBERING**

All subjects who sign an informed consent form (ICF) will be considered enrolled in the study and assigned a unique subject enrollment number not based on personally identifying information (PII). Each center will utilize a secure, site-controlled Master Subject Log in which the subjects PII will only be accessible to authorized research staff and will be linked to the uniquely assigned subject number.



## 7 DATA AND SAMPLE COLLECTION

### 7.1 DATA COLLECTION PROCESS

Data will be collected directly from subjects (via questionnaires and/or personal interview) when subjects visit a CARRA Registry site. When necessary, subjects may be contacted, or initiate contact themselves, via phone, mail or electronically by site staff or a call center to facilitate data collection. Appropriate protections of personally identifying information will be employed for all subject contact. Data collection may be supplemented by data extracted from the subject's medical record or EHR from dates on, before, between, and subsequent to baseline and follow up visits. Data collection may also be supplemented by linkage to administrative claims data or from other sources such as regional cancer registries, the National Death Index, claims databases maintained by government and commercial insurance providers, and other external data sources (e.g., health plans and health information networks, pharmacy records, laboratory test results, other patient registries). These linkages will be performed using identifying information, such as name, DOB, address, and SSN (if provided). Data will continue to be collected for the duration of subject's participation in the Registry.

#### 7.1.1 BASELINE DATA COLLECTION

After obtaining informed consent, essential data elements including demographics, disease phenotype, disease activity, and medication exposures will be obtained from subjects at enrollment. Data for the Registry will also be collected from the subject and/or parent/legal guardian, the site Principal Investigator (PI) or designee, and the medical record and/or EHR.

Baseline data collection may include:

- Current contact information for subject, parent/legal guardian, and additional individuals to enable long term follow up
- Demographic information
- Past medical history
- Disease diagnostic and/or classification category
- Family history
- Physician global assessment
- Associated conditions

- Current and previous medication exposures
- Physical examination data elements (height and weight)
- Disease specific data elements including disease activity and severity
- Comorbid conditions
- Subject/parent or legal guardian assessments
- Insurance information (including insurance identifiers), insurance claims data, and pharmacy benefit management data such as medications dispensed by pharmacies to the patient

#### 7.1.2 FOLLOW UP DATA COLLECTION

After enrollment, patients will be clinically evaluated as standard of care dictates, typically 2 to 6 times yearly. Follow-up (recurring) data will be collected directly from the subject (via paper or web-based questionnaires) and from the subject's medical record with the goal of entering data approximately every 6 months. Data may be collected more frequently in certain circumstances, for example, if the physician is treating a subject according to a consensus treatment plan. Data will also be collected each time treatment with a DMARD (biologic or non-biologic) is initiated.

Data may be obtained from the subject/legal guardian via telephone or other electronic means if subject is unable to visit the CARRA Registry site, or between scheduled visits. All appropriate protections will be employed for non-site subject contact.

Subjects may transfer clinical care during the course of this protocol from one CARRA Registry site to another CARRA Registry site. If this event occurs, the subject will be consented at the new CARRA Registry site in order to continue CARRA Registry participation.

If data have not been collected for  $\geq 9$  months and/or site investigators are unable to contact the patient, the CDCC may attempt to contact the subject/legal guardian to aid in data collection (see Section 7.1.5).

Follow-up Visit(s) data collection may include:

- Review of contact information
- Current and interval medication exposure
- Reasons for changes in medication regimen

- Physical exam data elements if during a clinic visit (height and weight)
- Disease specific data elements (including disease activity and severity)
- Physician global assessment
- SAEs
- ESIs of Common Terminology Criteria for Adverse Events grade 3 or above (unless otherwise specified, see Appendix C) irrespective of suspected causation
- Comorbid conditions
- Interval changes to Baseline Data
- Subject/parent or legal guardian assessments
- Insurance information (including insurance identifiers), insurance claims data, and pharmacy benefit management data such as medications dispensed by pharmacies to the patient

### 7.1.3 CARRA LEGACY REGISTRY DATA AND SAMPLES

All CARRA Legacy Registry (Protocol Number: CRNT\_REGST01) data and biospecimen samples will be included in this CARRA Registry database.

### 7.1.3 CONTACT INFORMATION

In order to facilitate communication and long-term follow-up, the subject and/or parent/legal guardian will be asked to provide relevant contact information for themselves and at least one individual (preferably more) outside the subject's primary residence who could be contacted by study staff in the event the subject cannot be reached. Typically, this information will be obtained during the baseline visit, although subject may bring this information to a subsequent visit. Accuracy of this information will be reviewed and updated at follow-up visits. Individuals other than the subject (or parent/legal guardian if the subject is a minor) will only be contacted in the event study staff cannot reach the study subject. When contacting other individuals, study staff will identify themselves by name and institution without revealing any subject's medical information. The sole purpose of contacting individuals other than the subject or parent/legal guardian is to obtain or verify the subject's current accurate contact information. This information will be entered electronically into a web-based research subject management platform.

#### 7.1.4 LONG-TERM FOLLOW-UP

Subjects may discontinue care at CARRA Registry sites for many reasons, including relocation or transition to adult rheumatology care (i.e., “aging out”). When this occurs, subjects will remain in the CARRA Registry through a systematic long-term follow-up program to which they consent to participate in at the time of enrollment.

Investigators will notify the CDCC by entering data into the electronic case report form (eCRF) when:

- Subjects are known to have discontinued care at their clinical sites, and/or
- The site has not collected data in >9 months and the site investigators are unable to contact the subject

The call center at the CDCC will then attempt to contact subjects to determine whether they continue to receive care at a CARRA Registry site and to encourage follow-up. If the subject is no longer receiving clinical care at a CARRA Registry site, he or she will be entered into the long term follow up program. If the subject wishes to withdraw consent for Registry participation, they will be free to do so. Study staff will indicate the date and reason for withdrawal in the research subject management platform and/or eCRF.

Once subjects enter the long-term follow-up program, the call center at the CDCC will call subjects every 6 months to collect data about interval medication exposures and safety events. The call center at CDCC will adhere to internal guidelines with regard to contacting and communicating with subjects for their scheduled follow-up visit. Safety events will be documented in a manner similar to events entered into the database by the sites. Subjects may contribute additional information as requested, (e.g., patient-reported outcomes, adverse event reports) and these data will be entered into an electronic data capture system.

#### 7.1.5 END OF STUDY OR WITHDRAWAL

Long-term follow-up will continue for at least 10 years; however, subjects or legal guardians can withdraw participation in the CARRA Registry at any time during the study, for any reason, without consequence. No special assessments will be required if the Registry is discontinued or a patient and/or parent/legal guardian opts to discontinue participation in the CARRA Registry. If subjects wish to discontinue from the Registry, they will be asked whether investigators may

continue to collect essential data elements from their medical records, noting that this activity does not involve direct contact with or time commitments from them. If the subject wishes to withdraw consent for Registry participation entirely, they will be free to do so. Site staff will indicate the date and reason for withdrawal in the eCRF.

## 7.2 OPTIONAL DATA AND SAMPLE COLLECTION

### 7.2.1 ADDITIONAL DATA COLLECTION

Social Security numbers (SSN) or other similar identification number as appropriate and insurance-specific identifiers will be collected from subjects willing to provide this information. This is optional and not mandatory for participation in the Registry. These identifiers will be collected to facilitate linkages with other data sources and stored separately from research data in the research subject management platform.

### 7.2.2 OPTIONAL SAMPLE COLLECTION

For subjects that provide appropriate consent, optional biospecimen samples may be collected at baseline and/or follow-up visits and sent to the CARRA Tissue Repository coordinating center or another laboratory associated with a CARRA site for processing and storage for future research on pediatric rheumatic disease.

Samples collected may include blood, urine, synovial fluid, buccal swabs, biopsy tissue, and other clinical specimens. Samples may be new specimens collected specifically for research purposes and/or may be leftover stand of care testing specimens that are salvaged prior to being discarded after local testing or use.

A subject and/or parent/legal guardian's decision about whether or not to provide samples does not affect his/her participation in the CARRA Registry.

### 7.2.3 COLLECTION OF OTHER ELECTRONIC DATA

To enhance the validity of data concerning medication use and important clinical outcomes (e.g., hospitalizations for serious adverse events), data from subjects enrolled in the CARRA Registry may be linked with data from other sources such as regional cancer registries, the National Death Index, claims databases maintained by government and commercial insurance providers, and other external data sources (e.g., health plans and health information networks, pharmacy records, laboratory test results, other patient registries). These linkages will be

performed using identifying information, such as name, DOB, address, and SSN (if provided) Examples of data that may be collected in this manner include information about outpatient pharmacy prescription fills, including the name, dose, and quantity of the medication and the date the medication was dispensed. These linked data will provide important information about treatments and outcomes in addition to the clinical information being collected in the Registry. Electronic data received that are considered identifiable will be governed by a Data Use Agreement that restricts use to qualified purposes, persons, and institutions.

## **8 ADVERSE EVENT COLLECTION AND FOLLOW-UP**

SAE collection and notification will be accomplished based on the assumption that expedited SAE reporting is exempt from investigational new drug regulations under FDA Code of Federal Regulations (CFR) Title 21, 312.2(b) because the therapeutics being studied are 1) lawfully marketed products not under investigational new drug regulations, 2) not investigational, 3) not under study in this protocol for a significant label change, 4) not under study in this protocol for a significant change in advertising, and 5) not under study in this protocol for a new route of administration or dosage level. SAEs will be collected and submitted to the Registry via EDC. Sites will report SAEs to the FDA according to institutional policies and procedures.

### **8.1. PROTOCOL-DEFINED SAFETY EVENTS**

This study will not capture all adverse events for patients enrolled in the Registry. It will only capture protocol-defined safety events that comprise SAEs and ESIs. ESIs may not meet the definition of SAE, but represent clinical events of particular concern. SAEs and ESIs are defined below.

1. SAEs meet one of the following criteria:
  - a. Fatal or life-threatening
  - b. Result in persistent or significant disability/incapacity
  - c. Constitute a congenital anomaly/birth defect
  - d. Require inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
  - Social reasons and/or respite care in the absence of deterioration in the patient's general condition
- e. Medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission)
2. Protocol-defined ESIs may include (see Appendix C for full list):
- a. Opportunistic infections (e.g., tuberculosis)
  - b. Optic neuritis
  - c. Demyelinating disease
  - d. New autoimmune disease
  - e. Malignancy
  - f. Uveitis
  - g. Cardiovascular events
  - h. Gastrointestinal perforation

In addition to SAEs and ESIs, the reason for discontinuation of biologic and non-biologic disease-modifying anti-rheumatic drugs will be collected. Discontinuation due to AEs that do not meet the definition of a SAE or ESI will be noted and may be analyzed to characterize existing or new safety signals. Discontinuations due to lack of effectiveness will also be noted.

Preexisting conditions identified during screening that worsen in severity or frequency during the study may also meet the criteria for safety events. In addition, all reports of the following special scenarios are considered AEs irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy
- Drug use during lactation or breast-feeding
- Lack of effectiveness
- Overdose

- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors
- Off-label use
- Withdrawal or rebound symptoms

## 8.2 IDENTIFICATION OF SAFETY EVENTS

Safety events will be prospectively identified and reported to the CDCC. Investigators will perform routine laboratory and other diagnostic tests to monitor for safety events at their discretion and in accordance with generally accepted medical practice for the duration of the study.

## 8.3 SAFETY EVENT CLASSIFICATION AND REPORTING

All SAEs and ESIs will be reported to the CDCC via the Registry by investigators upon learning of the event for reporting guidelines and report form. Investigators will submit an initial report that will include, at minimum: (1) an identifiable patient; (2) an identifiable reporter; (3) a suspect drug; (4) a specific SAE or ESI. This report will also note whether or not the patient is currently enrolled in an industry-sponsored study (e.g., a clinical trial). The minimum required elements will be collected using a rapid report form for SAEs and ESIs to enable timely forwarding from the CDCC to pharmaceutical companies; however, collection of additional information may occur subsequent to the initial report.

## 8.4 VERIFICATION OF SAFETY EVENTS

Whenever possible, the clinical investigator most knowledgeable about the patient and SAE or ESI will be contacted by the CDCC to ensure that the essential data elements collected are complete and accurate. If the subject has entered into the long-term follow-up program or the clinical investigators are unable to obtain the necessary details, then the CDCC will attempt to obtain information directly from the patient (see Section 7.1.5).

For selected SAEs and ESIs (e.g., death, TB, demyelinating disease, optic neuritis, uveitis), the CDCC will attempt to obtain copies of relevant medical records either from the site investigator or directly from the relevant hospital. Basic documents (e.g., hospital discharge summaries) will be obtained to verify the event. Once the relevant basic medical record documents are



obtained, the records will be redacted of all of the subjects' personal identifiers and the event will be verified by a medical monitor at the CDCC. This process will only be used to verify the occurrence of the event and will not be used to assess causality. If basic medical records to verify the event cannot be obtained, the event will be classified as "unverified" for the purposes of analysis. In addition, selected safety events, such as those that are very rare or prone to diagnostic uncertainty (e.g., malignancy), will be fully adjudicated via a more detailed medical record review (see Section 8.6).

## 8.5 EXTERNAL REPORTING OF SAFETY EVENTS

The external reporting of safety events will depend on the therapeutic agent(s) involved and the established agreements between the respective manufacturer(s) and the CARRA Registry. Pharmaceutical companies that financially support the Registry will be notified of all SAEs and ESIs that occur in subjects who have received medication(s) they manufacture to treat pediatric onset rheumatic disease. The Registry will report, at minimum, the 4 basic data elements of a safety report (an identifiable patient, an identifiable reporter, a suspected drug, and an AE) to the pharmaceutical companies in a sufficiently timely manner enabling pharmaceutical companies to fulfill regulatory guidelines for reporting events to health agencies. In these instances, the Registry will not report events directly to the FDA or other health agencies. Additional details about the event will be forwarded from the Registry to the manufacturer as necessary.

## 8.6 ADJUDICATION OF SELECTED EVENTS

Specific safety events that are uncommon or may involve diagnostic uncertainty will undergo review by an adjudication panel at the CDCC to confirm the event. The purpose of event adjudication is to verify the occurrence of the event, rather than to assess causality between biologic and non-biologic DMARD exposures and the safety event. Adjudicators will be blinded to medication exposures.

When an event that requires full adjudication is reported, the CDCC will request the relevant medical record documentation (e.g., for malignancy this would include biopsy results and corresponding physician notes confirming the occurrence of new malignancy). Once the relevant medical record documentation is obtained, the CDCC will redact the records of all of the subjects' personal identifiers (if not done so prior to receipt at the CDCC) and all mention of

biologic and nonbiologic DMARD use. The redacted records will then be forwarded to the adjudication panel for review. Prior to the review of any redacted records, a case definition will be developed for each outcome with specific criteria to categorize the certainty of the event (e.g., definite, probable, possible, more information needed). The results of the adjudication will be entered in to the CARRA Registry database with the corresponding event report.

## **9. DATA MANAGEMENT**

### **9.1 HARDWARE AND SOFTWARE CONFIGURATION**

#### **9.1.1 ELECTRONIC DATA CAPTURE**

Study data will be entered by site personnel and subjects into an EDC software platform. Submission of exported EHR data in a CDCC-approved electronic format may be an acceptable alternative for collection of data elements through the EHR (see Section 9.1.2), but a minimum of subject DOB or dummy DOB and gender will be entered via EDC in order to provide consistent EDC-level linkage with each subject's unique, coded CARRA Registry subject identifier.

#### **9.1.2 ELECTRONIC HEALTH RECORD DATA CAPTURE**

When available in the site EHR system, data from enrolled subjects corresponding to baseline and follow up study data collections may be extracted and transformed by the site into a mutually agreed upon electronic format. These data will be screened for accuracy and consistency (data quality assurance) by site personnel using manual and/or programmatic data cleaning processes. EHR data elements will be mapped to the corresponding study data elements. A joint analysis by site and CARRA Registry PIs or their designees will determine appropriate export mappings and data transformations. For certain data elements, supplemental data extraction from text (e.g. radiology or pathology reports) via natural language processing or similar algorithmic processes may be utilized using EHR data for which patient personal identifiers (other than the subject study identifier code) have been removed or obscured. Secure electronic transmission of EHR-derived Registry data exports to the CDCC or its designees will be utilized, including encrypted electronic file transfer or encrypted web services.

### 9.1.3 FEDERATED DATA ACCESS

Once Registry data has been entered into an EDC system or exported into electronic format from the EHR, edited and passed CDCC quality control measures, each participating site's data will be securely uploaded to a dedicated i2b2 system for each site. In addition to storage of the data elements themselves in the i2b2 data warehouse, metadata for individual data elements will be stored, including upload date and the originating source system. All i2b2 systems (one virtual machine per center) will be provisioned from a dedicated VMware VSphere cluster. Each CARRA Registry center PI will be able to access his/her site's data over an encrypted, secure connection using a unique username/password based authentication. Authorized investigators with appropriate access verified by their unique username/password combination will also be allowed to view statistical measures and aggregate information summarized across CARRA Registry centers.

### 9.1.3 SUBJECT CONTACT INFORMATION MANAGEMENT

All subject contact information will be treated as personally identifying information and securely stored under CARRA Registry site PI control utilizing a secure, web-based research subject management platform provided to the sites and managed by the CDCC (see Section 9.2.2). Subjects may be contacted by and/or on behalf of staff at their local site to inform them of eligibility for additional study protocols.

In addition to the site PI and his/her designates at each site, access to a subject's contact information will be accessible as necessary for follow-up activities by the CDCC Call Center. The CDCC Call Center, which facilitates collection of long-term clinical and safety data, including medication usage, hospitalizations, AEs or unexpected events, and PROs, will manage ongoing contacts with enrolled subjects in accordance with CARRA Registry policies. This will ensure retention and long-term follow-up as subjects move between medical providers and transition from pediatric to adult care. Subjects may withdraw consent for CARRA Registry follow-up at any time (see Section 7.1.6), in which case their contact information will be flagged as inactive and no further contact from the CDCC Call Center will occur.

### 9.1.4 STATISTICAL SOFTWARE

SAS, R, and S-PLUS statistical analysis software will be used for the analysis of data and statistical computations.

### 9.1.5 ACCESS CONTROL AND CONFIDENTIALITY PROCEDURES

Access to the electronic systems employed for collection of and access to CARRA Registry data will be managed via secure, centrally administered username/password authentication and authorization systems under direction of the CDCC. This protects the data from unauthorized changes, inadvertent loss or damage, and auditing of access to and use of these systems on a per-user basis.

### 9.1.6 SECURITY

Database and web servers will be secured by firewalls and through controlled physical access at the respective data centers. Security features ensure that any staff member accessing the database has the proper authority to perform the functions requested of the system. Within secondary databases, operating system level group-access control maintains similar security. Server resources for federated data access will be housed within a HIPAA-compliant data facility. Security audits are conducted on server and firewall connections per institutional standard operating procedures by the respective Information Services support staff at the CDCC and ancillary data facilities.

### 9.1.7 BACK-UP PROCEDURES

Database back-up will be performed daily or at other regular intervals according to CDCC protocols. Data will be retained according to CDCC policies and procedures.

### 9.1.8 VIRUS PROTECTION

Network services and software will be protected using virus-scanning software. Standard CDCC policies will be applied to regularly update these protection systems and respond to threat alerts.

## 9.2 SOURCES OF DATA

### 9.2.1 DESIGN AND DEVELOPMENT

The DCRI is the CDCC for this protocol and is responsible for development and programming of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site staff on data management procedures, data entry procedures for the EDC, and other relevant training. A web-based, distributed data entry

model will be implemented. For data exported in electronic format from study site EHR systems, the CDCC will assist the site in identifying a set of EHR data elements suitable for export, and the respective mappings from EHR to study data elements to be used for such electronic exports. The remainder of this section provides an overview of the data management plan associated with this protocol.

## 9.2.2 COLLECTION OF SUBJECT CONTACT INFORMATION

Research personnel at each site will be trained in the confidential collection and management of subject contact information, which will be treated as PII. PII will be stored in a web-based research subject management platform separately from other data collected for research purposes and will be accessible only by authorized staff at the center at which the subject is/was enrolled, the CDCC Call Center (see Section 9.1.4), and appropriately authorized CDCC research subject management platform administrators.

## 9.2.3 DATA ENTRY AND LONGITUDINAL DATA COLLECTION PROCESSES

**9.2.3.1 Data Collection via Electronic Case Report Forms.** The EDC process consists of direct data entry at the study sites into the EDC system(s) provided by the CDCC. Sites will enter data into eCRFs according to eCRF instructions provided and project-specific training. The investigator at each clinical site is responsible for maintaining accurate, complete and up-to-date records on his/her subjects, and for ensuring the completion of the eCRFs for each subject.

## 9.2.3.2 PATIENT-REPORTED OUTCOMES DATA COLLECTION

PROs will be obtained utilizing multiple modalities, including via paper, electronic, and telephone surveys, with electronic data entry by subjects preferred. Subjects or their parents/guardians will complete PROs either at the time of clinical research visits, periodically at other scheduled times from home, or ad-hoc related to the occurrence of events of interest. Paper-based PRO data will be entered into the EDC system by site or CDCC staff, as will data manually collected during telephone surveys by the CDCC Call Center. Electronic surveys will be stored in the respective electronic PRO system databases and then uploaded into the appropriate i2b2 data warehouse. Subjects or their parents/guardians will be made aware that they need to communicate directly to the treating physician about any specific problems or issues the subject may be having.

#### 9.2.3.3 DATA ACQUISITION VIA EHR DATA EXTRACTION

As an alternative to manual entry of study data via eCRFs, the study site may fulfill study data reporting requirements by electronic export of EHR data elements. The site will be responsible for identifying, extracting and transforming, and providing electronic export of EHR data corresponding to specific study data elements (see Section 9.1.2).

#### 9.2.3.4 DATA ACQUISITION VIA PATIENT OTHER REGISTRIES

The CDCC may receive subject data from other patient registries. These data may contain the subject's CARRA Registry ID or may be linked using patient identifiers.

#### 9.2.3.5 LINKAGE WITH OTHER ELECTRONIC DATA

Data from the Registry may be linked with data from other sources such as regional cancer registries, the National Death Index, claims databases maintained by government and commercial insurance providers, and other external data sources (e.g., health plans and health information networks, pharmacy records, laboratory test results, other patient registries). These linkages will be performed using identifying information, such as name, DOB, address, and, if provided, SSN or other insurance-specific identifiers.

The CDCC Call Center will function as an "honest broker" to perform the linkage between subjects in the Registry and their other electronic data. Call Center staff will obtain the personal identifiers to perform the linkage from the web-based research subject management platform in the same manner as they do to conduct telephone follow-up. The CDCC Call Center will not have access to the information in the clinical database, thus protecting the identity of Registry participants. Using personal identifiers, Call Center staff will perform linkages to supplemental data sources. They will add the subjects' study IDs to the supplemental data and remove PII from the data set. The resulting coded limited dataset will then be linked to Registry participants.

#### 9.2.3.6 COMPLIANCE WITH 21 CFR 11 ("ELECTRONIC RECORDS; ELECTRONIC SIGNATURES")

This study will collect data using eCRFs and a platform and process compliant with 21 CFR Part 11 for pharmacosurveillance activities. Prior to initiation of the study, each site will be assessed as to computer availability and internet connectivity to evaluate the capability of the site to use an EDC system. Data entry into eCRFs shall be performed only by authorized individuals.

Electronic CRFs will be monitored for completeness, accuracy, and attention to detail throughout the study. Electronic data entered directly by patients and/or parents/legal guardians (electronic PROs) will be collected and stored using a platform compliant with 21 CFR Part 11 when indicated for report of events and occurrences pertaining to pharmacosurveillance.

#### 9.2.4 DATA QUERYING AND EDITING

Collected data will be entered into the EDC system. If incomplete or inaccurate data are found, a data clarification request will be electronically generated by the EDC system or manually entered into the EDC system for site response. Sites will resolve EDC data inconsistencies and errors electronically in the EDC system. All data entry changes will be logged and available for subsequent audit.

#### 9.2.5 DATA QUALITY CONTROL PROCEDURES

The data management and site management teams will implement processes to oversee the quality of the data. The first level of quality control is during data entry into EDC systems. The sites will be trained on appropriate practices for data entry. The second level consists of programmatic consistency checks and/or range checks that are run on the data. Training will be made available to redress deficiencies and misunderstandings.

#### 9.2.6 DATA MANAGEMENT REPORTS

The CDCC will create standard data status reports detailing management volume, productivity, and completeness (current and overall). These reports will be generated at regular intervals for review by the study team.

### 9.3 CARRA TISSUE REPOSITORY

Blood and other biospecimens such as urine, cheek swab, stool samples, joint fluid and tissue samples that may be collected under this protocol will become part of the CARRA Tissue Repository. The CARRA Tissue Repository is a virtual repository and includes samples stored at Pediatric Rheumatology Tissue Repository at Cincinnati Children's Hospital Medical Center as well as other CARRA laboratories.

The CARRA Tissue Repository will transfer sample data to the CARRA Registry and an interface will be created to provide linkage of clinical and sample data. Access to the samples is tightly controlled and overseen by the CARRA Data and Sample Use Committee.

## **10 QUALITY CONTROL ACTIVITIES**

### **10.1 TRAINING SESSIONS AND PROCEDURES**

Training is an important method for ensuring study procedures are performed consistently, accurately and reliably. Site training is a primary component of this registry study and will include Investigator and Study Coordinator meetings held at least yearly via the web or face to face, teleconferences, study newsletters and a manual of operations, which will form the basis for site training and education. The CDCC will maintain records of all CDCC initiated training. Training sessions will be repeated periodically as required over the course of the study.

## **11 ANALYSIS PLAN**

This prospective observational registry will collect essential data about children with rheumatic diseases who are enrolled at CARRA Registry sites, irrespective of treatment. The goal duration of follow-up is 10 years for each patient. Descriptive statistics will be used to describe the CARRA Registry and evaluate the demographic and clinical characteristics of subjects, medication usage, incidence rates of SAEs and ESIs, and regional differences. In addition, the collected data will be sufficient to perform rigorous pharmacoepidemiologic safety studies of SAEs and ESIs. The aim of these analyses will be to estimate associations between individual therapeutic immunomodulatory agents and selected uncommon and delayed SAEs and ESIs, with consideration of confounding factors and effect modifiers. Data from the CARRA Registry will be used for a variety of different projects. Each project will develop its own statistical plan based on proposed use.

### **11.1 STATISTICAL DESIGN**

The Registry will collect essential data elements about disease phenotype, patient characteristics, medication use, and SAEs and ESIs for each subject as outlined in Section 8 and Appendix C. These data will be analyzed as described below. There is no maximum sample size; all eligible persons are candidates for inclusion in the safety registry.

### **11.2 SELECTION OF SUBJECTS FOR ANALYSES**

Data from the CARRA Registry may be used to satisfy post-marketing requirements and commitments to regulatory agencies. In this instance, individual patients will be prospectively



identified for future analyses at the time that they meet pre-specified inclusion criteria for the study (e.g., when they newly start the medication under study or newly start a medication with a similar indication). Alternatively, studies may also be performed using a retrospective cohort design (i.e., patients and comparators may be identified after data are collected but prior to data analyses).

### 11.3 DESCRIPTIVE ANALYSES

Descriptive analyses will report the demographic, disease phenotype/disease activity, medication exposures, SAE, and ESI information for all enrolled subjects. Overall incidence rates of SAEs and ESIs will be reported.

Company-specific data transfers regarding specific therapeutic agent(s) will be distributed to sponsors on a recurring basis. More detailed or specialized reports may be generated as part of agreements between the CARRA Registry and individual pharmaceutical industry collaborators or other stakeholders.

### 11.4 PHARMACOEPIDEMIOLOGIC SAFETY ANALYSES

Pharmacoepidemiologic safety analyses will include inference studies of the association between safety events and medication exposures. These analyses may be commissioned by collaborating pharmaceutical companies. Analysis plans for pharmacoepidemiologic safety studies will be developed jointly by the sponsoring pharmaceutical companies and the Scientific Oversight Committee. Analysis plans will be guided by the Guidelines for Good Pharmacoepidemiology Practices (International Society of Pharmacoepidemiology, 2008).

Verification of individual reports of SAEs and ESIs (and full adjudication, when indicated) will be performed prior to data analysis.

### 11.5 OTHER ANALYSES

Other data analyses (e.g., drug utilization studies, identification of patient factors associated with clinical outcomes) will be performed as scientifically appropriate. Analyses will be discussed with pharmaceutical company collaborators during the development of study specific design and analysis plans.

## 11.6 STATISTICAL METHODS

For descriptive analyses, statistics and reports (counts, medians, means, etc.) will be generated for demographic, disease phenotype/activity, medication exposure, SAE, and ESI information for all enrolled patients as detailed in the Statistical Analysis Plan.

General analysis plans for scientific publications will require the oversight and approval of the Registry Operations Committee and the CARRA Data and Sample Use Committee. Detailed analysis plans for industry-commissioned analyses will be reviewed with and approved by pharmaceutical company representatives.

Specific definitions for cohorts, exposures, and confounding variables will be determined prior to each pharmacoepidemiologic analysis. It is anticipated that cohort study designs will be used for most analyses. Whenever feasible, a “new user” design will be used for cohort studies. In this design, all patients in the study (including comparator patients) have initiated the therapy of interest at the start of follow-up. Data are specifically collected at the time of initiation of new therapeutic agents for this purpose. Confounding and effect modification will be considered in statistical models. Relevant sensitivity analyses, particularly of medication exposure risk windows, will be performed.

Statistical modeling approaches will be determined by the specific study question, but will likely include Cox proportional hazard or Poisson regression modeling for cohort studies. Simple comparisons of incidence rates (e.g., rate ratios or standardized incidence ratios) may be appropriate for very rare outcomes.

All medication exposures will be determined directly from CARRA Registry data and considered “as treated” in the primary analyses. Intention-to-treat or a time-limited last observation carried forward analysis may be included in secondary or sensitivity analyses.

## 12 STUDY RESPONSIBILITIES

Sites participating in CARRA studies are required to maintain overall regulatory requirements and general clinical/research education to qualify for continued participation in network research. The CDCC manages the regulatory document requirements for the CARRA Registry.

Before enrolling subjects, all site investigators and study staff having contact with human subjects or working with patient data will provide documentation of human subject protection (HSP) and Good Clinical Practices (GCP) training to the CDCC. They will participate in training on study protocol, requirements and procedures. All new staff added to the study will fulfill these same requirements.

Before approval to participate in the Registry study, all site PIs will be checked against the FDA lists of disqualified investigators, and if listed, will not be allowed to participate. Additionally, the CDCC will determine whether each site investigator has previously been inspected by FDA through a search of the public clinical investigator inspection list on FDA's website. Depending on the results of this search, a decision will be made by the CDCC regarding the participation of the investigator and the site. Sites and investigators also must meet the eligibility, performance, and activation requirements as outlined by the CDCC.

## 12.1 GENERAL PRINCIPLES

CARRA is a research network of pediatric rheumatologists and related investigators whose mission is to improve the health, well-being and outcomes of children and adolescents with rheumatic disease through fostering and facilitating collaborative research in prevention, treatment and cure.

## 12.2 CLINICAL AND DATA COORDINATING CENTER

Duke University (specifically, the DCRI) is the CDCC for the CARRA Registry and, where applicable, will work with the FDA, the NIH, CARRA, and public and private funding sources to:

- Provide project management, contracting, regulatory supervision, site management, data management, quality assurance, and site monitoring according to this protocol and any individual industry sponsor agreements.
- Manage contracts with sites, consultants, and subcontracts.

The CDCC will 1) develop a data management plan and will conduct data management activities, 2) provide final eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data, 5) monitor any preliminary analysis data clean-up activities, and 6) rigorously monitor final study data clean up prior to database lock.

### 12.3 INVESTIGATOR RESPONSIBILITIES

Site investigators will ensure that source documents for the CARRA Registry will be made available in a timely manner to the CDCC or health authority inspectors. Site investigators will be required to maintain subjects' clinical source documents that corroborate data collected on the eCRF as well as investigator study files. Additionally investigators shall:

1. Grant CDCC access to patient records to verify the entries on the eCRF
2. Ensure the accuracy, completeness, and timeliness of data reported to the CDCC in the eCRFs, including reporting of SAEs and ESIs
3. Assure appropriate safeguarding of subjects' protected health information (PHI)
4. Maintain adequate and accurate records to enable the study's conduct to be documented and its data to be subsequently verified. These documents should include the investigator's study file and patient clinical source documents, including the ICF. The investigator must keep these on file after completion or discontinuation of the study for the duration specified by the study contract and any local and federal regulations.
5. Ensure that all study staff are trained and qualified to perform the duties they are assigned to perform, consistent with the Site Delegation Log.
6. Comply with all applicable GCP, International Conference on Harmonization (ICH) and privacy laws.

Investigators agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of this Registry.

Investigators will provide current copies of the study protocol to all sub-investigators and other site personnel responsible for study conduct. They will also provide the CDCC with copies of all Institutional Review Board (IRB)/Independent Ethics Committee (IEC) actions regarding the Registry.

### 12.3.1 STUDY DATA REPORTING AND PROCESSING

All SAE's and ESI's recorded in the eCRF will be reviewed and electronically signed off by a site PI or sub-investigator to verify that he/she has reviewed the recorded data. The transfer of duties to a sub-investigator must be recorded on the Delegation list (kept on file at the site), and all sub-investigators must be listed on Site Delegation Log. The PI must ensure that all site staff involved in the conduct of the Registry are familiar with the protocol and the appropriate capture of all essential data elements.

### 12.3.2 TRAINING

The CDCC will train clinical site personnel, and the site PI will ensure that the site staff are qualified and trained to conduct the Registry according to the protocol. To ensure uniform data collection and protocol compliance, the CDCC will present a formal training session for Registry site personnel to include instructions for Registry procedures, data collection, schedules for follow-up with the study site coordinators, and regulatory requirements. The CDCC will provide detailed feedback about completion of eCRFs via regular reports.

### 12.3.3 MONITORING THE INVESTIGATIONAL SITES

The CDCC, as part of ongoing study management, will monitor site performance of CARRA Registry participation through routine central monitoring of data quality. The objectives of monitoring are to verify adherence to the protocol, proper patient enrollment and uniqueness, data completeness, and data consistency and accuracy. Additional objectives are to provide rapid, continuous assessment of site performance and rapid development and implementation of changes needed to maintain data quality, integrity, and high site performance.

The CDCC will provide initial training of all site investigators and coordinators before study initiation at any site. Centrally managed monitoring activities will verify the completeness and validity of all essential data elements using logic and range checks. Central monitoring is designed to assess how the clinical sites are performing overall and will determine the timing and urgency of other interventions. Additional training and site monitoring will be determined by site performance and addition of new site investigators or site coordinators.

Upon notice, sites will give the CDCC monitoring personnel reasonable access to the site's facilities and personnel to monitor and/or audit Registry data. The site PI and study coordinator

will be available, along with all documents supporting eCRF entries. Regulatory authorities may also audit the investigator during or after the study.

#### 12.3.4 DATA TRANSMITTAL AND RECORD RETENTION

Study sites will transcribe subject source data into eCRFs using a computerized EDC system that complies with all relevant aspects of 21 CFR Part 11. Edit checks, electronic queries, and audit trails are built into the system to ensure accurate, complete data collection. Data will be transmitted via secure Internet connection from investigational sites to a secure central database using industry-standard encryption modalities.

Copies of study-related documents will be retained at the site until notified by the CDCC that records may be destroyed.

#### 12.3.5 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the study according to the investigational plan (protocol) and/or the investigator agreement. All deviations will be reported to the CDCC and local IRB per institutional regulatory requirements.

#### 12.3.6 SITE CLOSEOUT

The CARRA Registry protocol does not have a defined end date. Data will be collected for all subjects with a goal of 10 years of follow-up per subject. The study will continue indefinitely as resources allow and continued need exists.

If the CARRA Registry were to cease data collection, or if an individual site is no longer able to participate, site closeout procedures will be performed. The CDCC will ensure that the site investigator's regulatory files are current and complete and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at site closeout include retention of study files, possibility of site audits, publication policies, and notifying the IRB of study closure.

### 12.4 DATA SHARING AND PUBLICATION POLICIES

Access to data will be consistent with the CARRA Data and Sample Use Committee policies (See <http://www.carragroup.org>). All requests for data analyses must be reviewed and

recommended by the CARRA Data Use Committee and approved by the CARRA Registry Operations Committee. Industry sponsors will have access to data query results, subject to the policies and procedures of the CARRA Registry Operations Committee and the CARRA Data and Sample Use Committee.

Industry sponsors will have a 30-day period to review all CARRA Registry publications and comment, query, or ask for further analyses, but cannot veto publication of analysis results.

All publications reflecting analysis of data from The CARRA Registry should conform to best practices in reporting observational studies, such as the guidelines of the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) initiative (<http://www.strobe-statement.org>).

## **13 ETHICAL CONSIDERATIONS**

### **13.1 ROLE OF CARRA**

CARRA has overall responsibility for the conduct of The CARRA Registry including assurance that it is consistent with post-marketing guidance documents from the FDA and other regulatory agencies, as appropriate. In this study, CARRA will have certain direct responsibilities and will delegate other responsibilities to the CDCC. CARRA and the CDCC will ensure compliance to international regulations and guidelines, including the Declaration of Helsinki, in the conduct of the Registry in centers outside of the US.

### **13.2 INFORMED CONSENT**

Before any study-related activities are initiated, informed consent will be obtained from all subjects who can provide legally effective consent. For subjects who are under the age of majority, informed consent will be obtained from a parent or legal guardian on the subject's behalf. Informed consent will be approved by the same IRB/IEC responsible for approval of this protocol. The ICF will conform to institutional requirements for informed consent and applicable regulations. When a study subject attains the age at which s/he can provide legally effective consent under applicable state law, the subject will be asked to provide informed consent on his/her own behalf.

### 13.3 CONFIDENTIALITY OF SUBJECTS

Subject confidentiality will be maintained throughout the Registry. A unique subject identification code will be used that allows linkage of all data reported for each subject.

Subject information, including PHI, collected in this study will comply with the standards for protection of privacy of PHI as promulgated in HIPAA and mandated in 45 CFR Parts 160 and 164. All records will be kept confidential and secure. Subject records, including PHI, will not be released to anyone other than the CDCC or its designees, authorized personnel at a subject's respective Registry site(s), and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that subjects' privacy is guaranteed.

### 13.4 SUBJECT CONTACT INFORMATION

Sites will treat all subject contact information as PII and store it securely under the Registry site PI's control in a web-based research subject management platform provided by the CDCC or its authorized designees. Clinical information entered by the sites will be stored separately from PII, with linkage between the two maintained via the unique subject identification code. The CDCC will treat all subject PII, including contact information, as confidential data that will be securely maintained.

### 13.5 MEDICAL RECORD DOCUMENTATION OF SAFETY EVENTS

When a SAE or ESI is reported to the CDCC, the corresponding site investigator will be contacted by the CDCC and asked to obtain the relevant basic documentation (or more detailed medical records if the event requires adjudication). Upon obtaining the necessary documents, the site investigator will submit records to the CDCC. If a site investigator is unable to obtain appropriate documents (or the subject has entered into the long term follow-up program), the CDCC will obtain the records directly. Redacted records will be forwarded for verification or adjudication, as required (see Section 8.6).

### 13.6 AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Every Registry subject (or his/her parent/guardian) will provide an authorization for use and disclosure of PHI under the HIPAA Privacy Rule (45 CFR 164.102 et seq) at the time of enrollment. It will be presented to, and signed by, the subject/parent or guardian at the same



time as the ICF. The investigator is responsible for obtaining subjects' (or parents'/guardians') authorizations and explaining the elements of the HIPAA authorization form.

HIPAA authorization may either be separate or included in the ICF, depending on local requirements. If a separate HIPAA document is signed, the investigator will append 1 signed original of each executed HIPAA Authorization to the subject's signed ICF and file it in the site's regulatory file. If a copy of the signed ICF is filed in the subject's medical records, a copy of the signed HIPAA Authorization form will be appended. Subjects will be given the signed duplicate for their personal records.

The investigator or the site will promptly inform the CDCC of any restrictions on the use or disclosure of PHI of any subject to which the site or the investigator have agreed under the Privacy Rule. The investigator or the site will also promptly inform the CDCC of any written revocation of any subject's HIPAA Authorization.

## **14 HUMAN SUBJECTS PROTECTION**

### **14.1 RESEARCH SUBJECT SELECTION AND JUSTIFICATION OF EXCLUSIONS**

All children meeting enrollment criteria as outlined in Section 5 will be eligible for participation.

### **14.2 RISKS/DISCOMFORTS OF STUDY PARTICIPATION**

Other than the usual risks associated with biospecimen collection, there are no physical risks to subjects in this observational registry.

The only risk is the potential compromise of PHI. PHI will be safeguarded by assignment of the unique subject identification code (see section 13.3) that will be used to identify all data reported to Registry for each subject. The linkage of subjects to their study ID will be securely maintained under the Registry site PI's control using the web-based research subject management platform (section 13.4).

### **14.3 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE REVIEW**

Before initiating this study, the protocol, site-specific informed consent/assent forms, HIPAA Authorization forms, recruitment materials, and other relevant information will be reviewed by the CDCC prior to submission to a properly constituted IRB/IEC at each participating clinical

site. It is anticipated that each IRB/IEC will adhere to ICH guidelines and 21 CFR 50 and 56 regulations outlining monitoring of the study and annual review. Documentation of IRB approval for this protocol, site-specific informed consent/assent forms, HIPAA Authorization forms, recruitment materials, subject questionnaires and any other material reviewed by the site's IRB/IEC will be retrieved and reviewed by the CDCC before site initiation. Any amendments to the protocol, approval of revisions to the informed consent documents, and any revisions to the protocol that may increase subject risk exposure (i.e., changes other than simple administrative and typographical changes) will be approved by each IRB/IEC before local implementation. The site investigator will provide the CDCC or its designee with documentation of all approvals.

#### 14.4 FINANCIAL DISCLOSURE

In accordance with requirements under 21 CFR 54, any listed or identified site investigator or sub-investigator (including the spouse and any dependent children of said individuals) directly involved in the treatment or evaluation of research subjects will disclose the following information for the time period during which the site investigator is participating in the Registry and for 1 year following the end of participation:

1. Any financial arrangement entered into between any pharmaceutical company and the investigator, whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study
2. Any other significant payments totaling >\$25,000, not including the costs of conducting this or other clinical studies, by any pharmaceutical company, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria
3. Any proprietary interest held by the investigator in any rheumatology immunomodulatory agent
4. Any significant equity interest in any pharmaceutical company, including ownership interest, stock options, or other financial interest whose value cannot be determined through reference to public prices (generally, interests in a non-publicly traded pharmaceutical company), or any equity interest in a publicly traded pharmaceutical company that exceeds \$50,000.

## **15 FUTURE STUDIES**

Health information collected in the CARRA Registry may be shared with researchers from other universities, the government, and drug or health-related companies for the purpose of conducting new research studies. Before any health information is shared for future research, the CARRA Data and Sample Use committee will review each application for scientific value and verify that an ethics review has been completed. To be approved by CARRA, any new research study will also have to be reviewed and approved by an IRB. If a research study is deemed exempt from local IRB review, supporting documentation must be submitted in lieu of an IRB approval. If a study is approved by the site's local IRB and CARRA, health information about research subjects will be shared with the researchers. PHI will not be disclosed without proper justification, IRB approval, and approval by the CARRA Data and Sample Use Committee.

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## 17 APPENDICES

### APPENDIX A: CARRA REGISTRY SUBJECT DISEASE ELIGIBILITY

#### **Juvenile Idiopathic Arthritis (JIA)**

A subject may be enrolled in the CARRA Registry with a diagnosis of JIA if he/she has arthritis of unknown etiology that begins before the 16<sup>th</sup> birthday and persists for at least 6 weeks, and other known conditions are excluded.

Categories of JIA according to the Edmonton International League of Associations for Rheumatology (ILAR) revised criteria will be used for this diagnosis. The principle of this classification is that all categories of JIA are mutually exclusive. This principle is reflected in the list of possible exclusions for each category. Any patient who meets the above general definition for JIA, and either 1) does not meet the specific criteria for a category or 2) meets the criteria for more than one criteria, should be considered as “undifferentiated”. The one exception is described below in the category of systemic arthritis.

#### Exclusions \*\*

The following exclusions will be referred to by letter (a, b, c, d, and/or e) for each category of JIA:

- a. Psoriasis or a history of psoriasis in the patient or first-degree relative
- b. Arthritis in an Human Leukocyte Antigen (HLA)-B27 positive male beginning after the 6th birthday.
- c. Ankylosing spondylitis, enthesitis-related arthritis (ERA), sacroiliitis with inflammatory bowel disease (IBD), Reiter’s syndrome (RS), or acute anterior uveitis AAU), or a history of one of these disorders in a first-degree relative.
- d. The presence of IgM rheumatoid factor (RF) on at least 2 occasions at least 3 months apart.
- e. The presence of systemic JIA (sJIA) in the patient.

The application of the above exclusions is indicated under each JIA category listed below, and may change as new data become available.

Categories	Definition
Systemic Arthritis	<p>Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following:</p> <ul style="list-style-type: none"> <li>a. Evanescent (non-fixed) erythematous rash</li> <li>b. Generalized lymph node enlargement</li> <li>c. Hepatomegaly and/or splenomegaly</li> <li>d. Serositis</li> </ul> <p>Exclusions: a, b, c, d. **</p> <p>*Exception: arthritis need only be present for 10 days w/new onset systemic arthritis.</p>
Oligoarthritis	<p>Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized:</p> <ul style="list-style-type: none"> <li>a. Persistent oligoarthritis: Affecting not more than 4 joints throughout the disease course</li> <li>b. Extended oligoarthritis: Affecting a total of more than 4 joints after the first 6 months of disease</li> </ul> <p>Exclusions: a, b, c, d, e. **</p>
Polyarthritis (Rheumatoid Factor Negative)	<p>Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.</p> <p>Exclusions: a, b, c, d, e. **</p>
Polyarthritis (Rheumatoid Factor Positive)	<p>Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.</p> <p>Exclusions: a, b, c, e. **</p>
Psoriatic Arthritis	<p>Arthritis and psoriasis, or arthritis and at least 2 of the following:</p> <ul style="list-style-type: none"> <li>a. Dactylitis</li> <li>b. Nail pitting or onycholysis</li> <li>c. Psoriasis in a first-degree relative</li> </ul> <p>Exclusions: b, c, d, e. **</p>



Categories	Definition
Enthesitis Related Arthritis (ERA)	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: <ol style="list-style-type: none"> <li>a. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain</li> <li>b. The presence of HLA-B27 antigen</li> <li>c. Onset of arthritis in a male over 6 years of age</li> <li>d. Acute (symptomatic) anterior uveitis (AAU)</li> <li>e. History of ankylosing spondylitis, ERA, sacroiliitis with IBD, RS, or AAU in a first-degree relative</li> </ol> Exclusions: a, d, e. **
Undifferentiated Arthritis	Arthritis that fulfills criteria in no category above or in 2 or more of the above categories.

**References:**

MedicalCRITERIA.com; Editor, Guillermo Firman, M.D. ILAR Classification Criteria for Juvenile Idiopathic Arthritis. (Accessed January 2, 2014 at [WWW.MEDICALCRITERIA.COM/SITE/EN/CRITERIA/79-RHEUMATOLOGY/339-REUJIA.HTML](http://WWW.MEDICALCRITERIA.COM/SITE/EN/CRITERIA/79-RHEUMATOLOGY/339-REUJIA.HTML))

**Juvenile Ankylosing Spondylitis**

A subject may be enrolled in the CARRA Registry with a diagnosis of **Juvenile Ankylosing Spondylitis** if he/she has a clinical diagnosis of undifferentiated spondyloarthropathy, juvenile ankylosing spondylitis, psoriatic arthritis, reactive arthritis or spondylitis of inflammatory bowel diseases. Subject must have onset of disease symptoms prior to his/her 18<sup>th</sup> birthday and must have radiologic evidence of bilateral inflammation of the sacroiliac joints.

**Probable Systemic Juvenile Idiopathic Arthritis (sJIA)**

A subject may be enrolled in the CARRA Registry with a diagnosis of probable sJIA if he/she is under the age of 18 and has:

- Fever for at least 2 weeks
- Arthritis in one or more joints for at least 10 days
- At least one of the following:
  - Evanescent erythematous rash
  - Generalized lymphadenopathy

- Hepatomegaly and/or splenomegaly
- Pericarditis, pleuritis and/or peritonitis

**Systemic Lupus Erythematosus (SLE)**

A subject may be enrolled in the CARRA Registry with a diagnosis of SLE if he/she has onset of symptoms prior to his/her 18<sup>th</sup> birthday and if:

- 4 or more of the 11 criteria below are present,  
Or
- 3 of the 11 criteria below are present, if one of the criterion is “Renal Disorder” and subject has biopsy proven lupus nephritis

Criteria may be present serially or simultaneously during any interval of observation.

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	a) Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion  OR  b) Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	a) Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed  OR  b) Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed

Criterion	Definition
8. Neurologic Disorder	a) Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	a) Hemolytic anemia-with reticulocytosis OR b) Leukopenia-< 4,000/mm <sup>3</sup> on 2 occasions OR c) Lymphopenia-< 1,500/ mm <sup>3</sup> on 2 occasions OR d) Thrombocytopenia-<100,000/ mm <sup>3</sup> in the absence of offending drugs
10. Immunologic Disorder	a) Anti-DNA: antibody to native DNA in abnormal titer OR b) Anti-Sm: presence of antibody to Sm nuclear antigen OR c) Positive finding of antiphospholipid antibodies on: an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, or d) A false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

**References:**

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;40:1725.

Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.

## **Primary Sjogren's Syndrome Criterion**

A subject may be enrolled in the CARRA Registry with a diagnosis of Primary Sjogren's Syndrome if he/she has onset of symptoms prior to the 18<sup>th</sup> birthday, does not have a potentially associated rheumatic disease, does not have any of the exclusion criteria noted below, and has either:

- a. The presence of any 4 of the 6 items below, as long as either item IV (Histopathology) or VI (Serology) is positive,
  - a. or
- b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)

### **I. Ocular symptoms: a positive response to at least one of the following questions:**

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

### **II. Oral symptoms: a positive response to at least one of the following questions:**

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

### **III. Ocular signs-that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:**

1. Schirmer's I test, performed without anesthesia ( $\leq 5$  mm in 5 minutes)
2. Rose bengal score or other ocular dye score ( $\geq 4$  according to van Bijsterveld's scoring system)

### **IV. Histopathology**

In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue

## **V. Salivary gland involvement**

Objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

- a. Unstimulated whole salivary flow ( $\leq 1.5$  ml in 15 minutes)
- b. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
- c. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

## **VI. Autoantibodies: presence in the serum of the following autoantibodies:**

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

### **Exclusion Criteria:**

- a) Past head and neck radiation treatment
- b) Hepatitis C infection
- c) Acquired immunodeficiency disease (AIDS)
- d) Pre-existing lymphoma
- e) Sarcoidosis
- f) Graft versus host disease
- g) Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug)

### **References**

Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH; European Study Group on Classification Criteria for Sjogren's Syndrome. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002 Jun;61(6):554-8.

## **Mixed Connective Tissue Disease (MCTD)**

A subject may be enrolled in the CARRA Registry with a diagnosis MCTD if he/she has onset of symptoms prior to the 18<sup>th</sup> birthday and has:

- Positive anti U1 RNP at hemagglutination titer > 1:160,  
AND
- Three of the following clinical criteria:
  1. Edema of hands
  2. Synovitis
  3. Myositis
  4. Raynaud's
  5. Acrosclerosis

\*If the three clinical criteria are hand edema, Raynaud's and acrosclerosis (1, 4, and 5), diagnosis requires at least one other feature.

*Adapted from the 1989 Alarcon-Segovia Diagnostic Criteria for Mixed Connective Tissue Disease*

## **Juvenile Dermatomyositis (JDM)**

A subject may be enrolled in the CARRA Registry with a diagnosis of JDM if he/she has onset of symptoms prior to the 18th birthday and meets criteria for definite JDM, probably JDM, or amyopathic JDM as defined below.

### **Definite JDM**

Classic skin involvement for JDM, and at least 3 of the following:

- a. Muscle weakness
- b. Elevation of muscle enzyme(s)
- c. Abnormal EMG suggestive of inflammatory myopathy
- d. Abnormal muscle biopsy suggestive of inflammatory myopathy
- e. MRI evidence of myositis

### **References**

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med.1975;292(8):403-7.
2. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med.1975;292(7):344-7.

### **Probable JDM**

Probable JDM will be diagnosed in those cases where the treating pediatric rheumatologist has diagnosed JDM, where the definite criteria are not met, but the following criteria are met;

a. Physician diagnosis of JDM based on **BOTH** of:

1. Typical Rash (Gottron's, heliotrope, extensor surface rash, periungual telangiectasia)

**AND**

2. Evidence of muscle involvement (weakness, muscle enzymes, imaging, biopsy, EMG)

b. No other explanation for findings (e.g. Infection, endocrinopathy, SLE, MCTD, juvenile idiopathic arthritis, AAV, etc.)

### **Amyopathic JDM**

Amyopathic JDM may be diagnosed in those individuals who do not meet above criteria for definite or probable JDM because of absence of muscle involvement. Amyopathic JDM must meet all the following criteria:

a. Rash typical for JDM

b. Normal muscle enzymes

c. No muscle weakness

d. Negative muscle involvement by at least 1 of (preferably more) MRI, EMG or muscle biopsy

e. Age < 18

### **Systemic Sclerosis (Modified ACR Classification of Systemic Sclerosis)**

A subject may be enrolled in the CARRA Registry with a diagnosis of systemic sclerosis if he/she has onset of symptoms prior to the 18th birthday and has either one major or two minor criteria as outlined below.

#### **Major criterion:**

a. Proximal scleroderma (proximal to MCPs/MTPs, e.g., face, forearms, trunk – manifesting as tightness, thickening, non-pitting induration, excluding localized forms of scleroderma)

**Minor criteria:**

- a. Cutaneous
- b. Sclerodactyly
- c. Peripheral vascular
  - 1. Raynaud's phenomenon
  - 2. Nailfold capillary abnormalities
  - 3. Digital tip ulcers
- d. Gastrointestinal
  - 1. Dysphagia
  - 2. Gastroesophageal reflux
- e. Cardiac
  - 1. Arrhythmias
  - 2. Heart failure
- f. Renal
  - 1. Renal crisis
  - 2. New-onset arterial hypertension
- g. Respiratory
  - 1. Pulmonary fibrosis (HRCT/radiography)
  - 2. Decreased DLCO
  - 3. Pulmonary arterial hypertension
- h. Neurologic
  - 1. Neuropathy
  - 2. Carpal tunnel syndrome
- i. Musculoskeletal
  - 1. Tendon friction rubs
  - 2. Arthritis
  - 3. Myositis
- j. Serologic
  - 1. Antinuclear antibodies
  - 2. SSc-selective autoantibodies (anticentromere, anti-topoisomerase I [Scl-70], antifibrillar, anti-PMScl, antifibrillin or anti-RNA polymerase I or III)

\* HRCT = high-resolution computed tomography



DLCO = diffusing capacity for carbon monoxide.

## References

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-90. Lonzetti LS et al. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. *Arthritis Rheum* 2001;44:735-38.

Zulian F, Woo P, Athreya BH, Laxer RM, Medsger, Jr. TA, Lehman TAJ, Cerinic MM, Martini G, Ravelli A, Russo R, Cuttica R, de Oliveira SKF, Denton CP, Cozzi F, Foeldvaril I, Ruperto N, for the Pediatric Rheumatology European Society/American College of Rheumatology/European League Against Rheumatism AD HOC Committee on Classification Criteria for Juvenile Systemic Sclerosis “**The Pediatric Rheumatology European Society/ American College of Rheumatology/European League Against Rheumatism Provisional Classification Criteria for Juvenile Systemic Sclerosis**” *Arthritis & Rheumatism (Arthritis Care & Research)* 57(2): March 15, 2007, pp 203–212 DOI 10.1002/art.22551 © 2007, American College of Rheumatology.

This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the criteria set has been quantitatively validated using patient data, but it has not undergone validation based on an external data set. All American College of Rheumatology -approved criteria sets are expected to undergo intermittent updates.

## **Localized Scleroderma**

A subject may be enrolled in the CARRA Registry with a diagnosis of localized scleroderma if he/she has onset of symptoms prior to the 18th birthday and has localized induration of the skin and subcutaneous tissue characterized by sclerosis. The diagnosis must be made clinically by an experienced physician, or on skin biopsy.

## **Vasculitis**

A subject may be enrolled in the CARRA Registry with a diagnosis of vasculitis if he/she has onset of symptoms prior to the 18<sup>th</sup> birthday and meets criteria for any of the vasculitides below:

Validated Pediatric Specific Criteria (Ozen et al, 2010) used are:

### **Childhood Polyarteritis Nodosa**

Requires a systemic inflammatory disease with evidence of necrotizing vasculitis OR angiographic abnormalities of medium/small sized arteries (mandatory criterion) plus 1 of 5 criteria:

- a. Skin involvement
- b. Myalgia/muscle tenderness
- c. Hypertension
- d. Peripheral neuropathy
- e. Renal involvement

### **Childhood Wegener's Granulomatosis**

Requires 3 of 6 criteria:

- a. Histopathologic evidence of granulomatous inflammation
- b. Upper airway involvement
- c. Laryngo-tracheo-bronchial involvement
- d. Pulmonary involvement (X ray/CT)
- e. ANCA positivity
- f. Renal involvement

### **Childhood Takayasu's Arteritis**

Requires typical angiographic abnormalities of the aorta or its main branches and pulmonary arteries (mandatory criterion) plus 1 of 5 criteria:

- a. Pulse deficit or claudication
- b. Blood pressure discrepancy in any limb
- c. Bruits
- d. Hypertension

- e. Elevated acute phase reactant

### **Kawasaki Disease**

Fever persisting at least 5 days and the presence of at least 4 of the following 5 principal features:

1. Changes in extremities:
  - a. Acute: Erythema and edema of hands and feet
  - b. Convalescent: Membranous desquamation of fingertips
2. Polymorphous exanthema
3. Bilateral, painless bulbar conjunctival injection without exudate
4. Changes in lips and oral cavity: Erythema and cracking of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
5. Cervical lymphadenopathy ( $\geq 1.5$  cm in diameter), usually unilateral

\*Patients with fever and fewer than 4 principal symptoms can be diagnosed as having Kawasaki disease when coronary artery disease is detected by 2-dimensional echocardiography or coronary angiography. Other diagnoses should be excluded. The physician should be aware that some children with illness not fulfilling these criteria have developed coronary artery aneurysms.

### **Vasculitides without Specific Pediatric Criteria**

Microscopic Polyangiitis:

- a. Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules, or arterioles).
- b. Necrotizing arteritis involving small and medium-sized arteries may be present.
- c. Necrotizing glomerulonephritis is very common.
- d. Pulmonary capillaritis often occurs.
- e. Often associated with positive ANCA. (Jennette 1997, Watts, 2007)

### **Primary Central Nervous System Vasculitis**

- a. Any newly acquired neurological and/or psychiatric deficit Plus angiography and or brain biopsy evidence of CNS vasculitis, in the absence of a systemic condition known to cause, be associated or mimic CNS vasculitis (Elbers 2008, Calabrese and Mallek, 1988)

- b. Other primary vasculitis could include Churg-Strauss vasculitis, cutaneous polyarteritis, hypocomplementemic vasculitis, Behcet's syndrome, etc.

### **Cutaneous polyarteritis nodosa**

- a. Cutaneous manifestations: subcutaneous nodules, livedo, purpura, ulcers AND
  - b. Histopathological findings: fibrinoid necrotizing vasculitis of small and medium-sized arteries
- AND**
- c. Exclusion of systemic or organ system involvement, neuropathy, arthritis, hypertension

### **Behcet's syndrome**

The international criteria include recurrent oral ulcerations, plus 2 of the following:

- a. Recurrent genital ulcerations
- b. Eye lesions
  - 1. anterior uveitis
  - 2. posterior uveitis
- c. Cells in vitreous
- d. Retinal vasculitis
- e. Skin lesions
  - 1. Erythema nodosum
  - 2. Pseudofolliculitis
  - 3. Papulopustular lesions
  - 4. Acneiform nodules (in a post-adolescent patient not taking steroids)
- f. Positive pathergy test

### **Churg-Strauss syndrome (CSS)**

Classified as CSS if at least four of six criteria are present:

- a. Asthma: History of wheezing or diffuse high-pitched expiratory rhonchi.
- b. Eosinophilia: Eosinophilia >10% on differential white blood cell count.
- c. Mono- or polyneuropathy: Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (glove/ stocking distribution) attributable to systemic vasculitis.
- d. Pulmonary infiltrates, non-fixed: Migratory or transitory pulmonary infiltrates (not including fixed infiltrates) attributable to vasculitis.

- e. Paranasal sinus abnormality: History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses.
- f. Extravascular eosinophils: Biopsy including artery, arteriole or venule showing accumulations of eosinophils in extravascular areas.

Other primary vasculitis could include cutaneous polyarteritis, hypocomplementemic vasculitis.

## References

Ozen et al: The EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener Granulomatosis, and childhood Takayasu arteritis: Ankara 2008. PART II: Final Classification Criteria. *Ann Rheum Dis*, 2010.

Jennette JC and Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997; 337(21): 1512-23.

Watts R, Lane S, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; 66(2): 222-7.

Calabrese LH and Mallek JA.. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine (Baltimore)* 1988; 67(1): 20-39.

Elbers J and Benseler SM. Central nervous system vasculitis in children. *Curr Op Rheum* 2008; 20: 47-54.

American Heart Association. Diagnostic Guidelines for Kawasaki Disease. *Circulation*. 2001;103:335-336.

## **Sarcoid**

A subject may be enrolled in the CARRA Registry with a diagnosis of sarcoid if he/she has onset of symptoms prior to the 18<sup>th</sup> birthday and has both the following:

- a. Clinical and radiologic features consistent with sarcoid, *and/or*
- b. Non-caseating granulomas demonstrated histologically

## **Reference**

Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153-65.

## **Fibromyalgia**

A subject may be enrolled in the CARRA Registry with a diagnosis of fibromyalgia if he/she has onset of symptoms prior to the 18th birthday and meets either ACR or Yunus and Masi diagnostic criteria for fibromyalgia.

1990 ACR Criteria for the Classification of Fibromyalgia\*:

a. History of widespread pain. By definition:

1. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist.
2. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present.
3. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

b. Pain in 11 of 18 tender point sites on digital palpation. By definition, pain on digital palpation, must be present in at least 11 of the following 18 sites:

1. Occiput: Bilateral, at the suboccipital muscle insertions.
2. Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
3. Trapezius: bilateral, at the midpoint of the upper border.
4. Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
5. Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
6. Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
7. Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.

8. Greater trochanter: bilateral, posterior to the trochanteric prominence.
9. Knee: bilateral, at the medial fat pad proximal to the joint line.

Digital palpation should be performed with an approximate force of 4 kg.

For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender is not to be considered "painful."

\*For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

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### **1990 Yunus and Masi Diagnostic Criteria for Juvenile Primary Fibromyalgia Syndrome**

Diagnostic criteria:

- a. Three or more months of widespread musculoskeletal pain defined as three or more pain locations.
  - b. Five or more well defined tender point sites\*
  - c. The absence of underlying medical condition causes for the symptoms
  - d. Routine laboratory test results in normal range
  - e. Presence of 3 of the following 10 minor criteria (also referred to as associated symptoms) as stated below:\*
1. Chronic anxiety or tension
  2. Fatigue
  3. Poor sleep
  4. Chronic headaches
  5. Irritable bowel syndrome
  6. Subjective soft tissue swelling
  7. Numbness/tingling of extremities
  8. Pain modulation by physical activities
  9. Pain modulation by weather conditions

#### 10. Pain modulation by anxiety or stress

\*For classification purposes, if patients have 5 minor criteria, the presence of 4 tender points is all that is required to make a diagnosis of fibromyalgia.

Yunus MB, Masi AT. Juvenile primary fibromyalgia syndrome. A clinical study of thirty-three patients and matched normal controls. *Arthritis Rheum* 1985;28(2):138-45.

### **Auto-inflammatory Diseases**

A subject may be enrolled in the CARRA Registry with a diagnosis of autoinflammatory disease if he/she has onset prior to the 18<sup>th</sup> birthday. Autoinflammatory diseases comprise a heterogeneous group of inherited diseases of uncertain pathogenesis, in which the diagnosis is based on clinical features and/or genetic testing and include:

- a. Periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome
- b. TRAPS (TNF receptor-associated periodic syndrome)
- c. Muckle-Wells syndrome
- d. AS (familial cold autoinflammatory syndrome)
- e. Neonatal-onset multisystem inflammatory disease
- f. Chronic infantile neurological cutaneous and articular syndrome
- g. CH (Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome)
- h. Muckle-Wells syndrome or Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome
- i. Familial Mediterranean fever
- j. Hyperimmunoglobulin (Ig) D syndrome
- k. Deficiency of interleukin-1 receptor antagonist
- l. Chronic recurrent multifocal osteomyelitis
- m. Synovitis, acne, pustulosis, hylarostosis, osteitis
- n. Majeed syndrome
- o. Unknown origin
- p. Other

### **Idiopathic Uveitis**

A subject may be enrolled in the CARRA Registry with a diagnosis of idiopathic uveitis if he/she has onset prior to the 18<sup>th</sup> birthday and there is no known cause or related rheumatic condition. If subject has another rheumatic disease, enroll him/her in the Registry with a primary diagnosis of the other rheumatic disease, not idiopathic uveitis.



The definition of uveitis refers to inflammation of the middle layer of the eye, termed the "uvea" but in common usage may refer to any inflammatory process involving the interior of the eye. Uveitis may be classified anatomically into anterior, intermediate, posterior and panuveitic forms, based on which part of the eye is primarily affected by the inflammation.

## APPENDIX B: JIA DATA ELEMENTS COLLECTED AT ENROLLMENT

### Demographics

- Comprehensive contact details
- DOB
- Sex
- Race
- Comorbid medical conditions

### Disease Phenotype/History

- Year of diagnosis
- Physician-assigned JIA category
- Other chronic medical conditions (e.g., diabetes mellitus, asthma, celiac disease, autoimmune thyroid disease, primary immunodeficiency)

### Disease Activity/Severity

- Parent's global assessment of overall well-being
- Physician's global assessment of disease activity
- Total number of currently active joints
- JADAS-10
- Erythrocyte sedimentation rate or C-reactive protein (with normal range) (if available)
- Active uveitis or active topical glucocorticoid therapy for uveitis (including influence on the occurrence / treatment of uveitis)
- Presence of active systemic features: fever, evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly or splenomegaly, serositis

### Medication Exposures

- Start and stop dates (month/year) for all JIA medications received within past 12 months of enrollment
- Dose and frequency of current medications (at the start of the visit, not newly prescribed at this visit)
- Dispense history of medications
- Reason for discontinuation of medications within the last 12 months (lack of desired effect, AE, fear of potential SAE, difficulty with administration, clinical improvement, financial cost)
- "Ever/Never" exposed for medications received >12 months before enrollment
- Note medications newly prescribed at this visit

- Subspecialty of medication prescriber
- List of included JIA medications:
  - Abatacept
  - Adalimumab
  - Anakinra
  - Azathioprine
  - Canakinumab
  - Certolizumab
  - Cyclophosphamide
  - Cyclosporine A
  - Etanercept
  - Gold
  - Golimumab
  - Glucocorticoids, intra-articular
  - Glucocorticoids, oral (chronic daily for >1 month)
  - Glucocorticoids, intravenous
  - Hydroxychloroquine
  - Infliximab
  - Intravenous immunoglobulin
  - Leflunomide
  - Lenalidomide
  - Methotrexate
  - Mycophenolate mofetil
  - NSAIDs, chronic daily
  - Rilonacept
  - Rituximab
  - Sulfasalazine
  - Tacrolimus
  - Thalidomide
  - Tocilizumab
  - Tofacitinib
  - Ustekinumab

## JIA Data Elements Collected Every 6 Months and at Change in Medication

### **Demographics**

- Comprehensive contact details
- Comorbid medical conditions [*same as for baseline*]

### **Disease Phenotype/History**

- Physician-assigned JIA category
- Other chronic medical conditions (e.g., diabetes mellitus, asthma, celiac disease, autoimmune thyroid disease, primary immunodeficiency)

### **Disease Activity/Severity**

- Parent's global assessment of overall well-being
- Physician's global assessment of disease activity
- Total number of currently active joints
- JADAS-10
- Erythrocyte sedimentation rate or C-reactive protein (with normal range) (if available)
- Active uveitis or active topical glucocorticoid therapy for uveitis (to allow assessment of influence of therapy on the occurrence / treatment of uveitis)
- Presence of active systemic features: fever, evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly or splenomegaly, serositis

### **Medication Exposures**

- [*List of medications same as above*]
- Start and stop dates (month/year) for all JIA medications received since last data entry
- Dose and frequency of current medications (at the start of the visit, not newly prescribed at this visit)
- Dispense history of medications
- Reason for discontinuation of any medications since last data entry (lack of desired effect, adverse event, clinical improvement, financial cost, fear of potential serious adverse event, difficulty with administration)
- Note medications newly prescribed at this visit
- Subspecialty of medication prescriber

## Essential Data Elements for Safety Events

- Event onset date
- Event description
- Event diagnosis, linked to Medical Dictionary for Regulatory Activities (MedDRA) terms
- Event severity (Common Terminology Criteria for Adverse Events-level)
- Event seriousness (meets/does not meet SAE definition)
- All current medications
- Actions taken with current immunomodulatory medications (withdrawn, reduced, increased, unchanged)
- Physician judgment about relationship of medications to event (probable, possible, unlikely)
- Event time course, duration
- Information about de-challenge or re-challenge experience
- Event outcome

## APPENDIX C: EVENTS OF SPECIAL INTEREST

Events of special interest may include:

- Mycobacterium tuberculosis infection
- Progressive multifocal leukoencephalopathy (JC virus)
- Other opportunistic infections (e.g., Legionella, Listeria, systemic infections due to endemic mycoses (Coccidioides, Blastomyces, Histoplasma), Pneumocystis, Aspergillus, Nocardia, Cryptococcus, Toxoplasma)
- Any malignancy
- Optic neuritis
- Demyelinating disease
- Pulmonary hypertension
- Interstitial lung disease
- Pulmonary alveolar proteinosis
- Lipoid pneumonia
- Cardiovascular event (myocardial infarction or stroke)
- New autoimmune disease (e.g., systemic lupus erythematosus)
- Pregnancy and pregnancy outcomes
- Uveitis
- Inflammatory bowel disease
- Leukopenia
- Neutropenia
- Thrombocytopenia
- Aplastic anemia
- Macrophage activation syndrome
- Hepatitis
- Hypercholesterolemia
- Gastrointestinal perforation
- Severe injection site reactions
- Infections treated with IV anti-infectives
- Anaphylaxis/Hypersensitivity reactions
- Bleeding events requiring transfusion or hospital evaluation
- Hepatic events
- Additional events to be added as needed