An Open Label, Multi-Center, Phase 3 Efficacy Study of Sub-Q Abatacept (Orencia) in Preventing Extension of Oligoarticular Juvenile Idiopathic Arthritis JIA (Limit-JIA)

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Protocol Version and Amendment Tracking

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Protocol Version 1.0	20December2018
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PROTOCOL SYNOPSIS

Protocol Number	Version 5.0
Protocol Title	An, Open Label, Multi-Center, Phase 3 Efficacy Study of Sub-Q Abatacept (Orencia) in Preventing Extension of Oligoarticular JIA (Limit-JIA)
Main Criteria for Inclusion	• Age ≥ 2 years old and ≤ 16.5 years old • Clinical diagnosis of JIA by a pediatric rheumatologist within the past 6 months • Arthritis affecting ≤ 4 joints between disease onset and enrollment • Prior or concurrent enrollment in the CARRA Registry • Weight ≥50 kg (Canadian Sites only)
Study Objective	To evaluate the effectiveness of a 24-dose course of weekly treatment with a T-cell co-stimulation inhibitor (abatacept (Orencia)) plus usual care versus usual care subjects from the CARRA Registry to prevent polyarthritis (≥5 joints), uveitis, or treatment with other systemic medication (s) for JIA (i.e. one or more of the following: systemic glucocorticoids, DMARD or biologic) medication within 12 months of enrollment in children with recent-onset limited JIA
Study Design	Prospective, open-label clinical trial. with stratified enrollment of participants based upon baseline risk of developing polyarthritis or uveitis
Treatment Regimen	• Abatacept (Orencia) plus usual care for 24 weekly doses with ongoing usual care and 24 weeks of follow up for a total of 48 weeks. • Usual care for 12 months (48 weeks) as recorded in the CARRA Registry • Usual care is defined as NSAIDs and/or intra-articular glucocorticoids at the discretion of the treating provider
Duration of Study Participation	12 months (48 weeks)
End -of Study- Definition	Date of last study participant's last visit
Number of Study Participants	89
Number of Sites	Up to 30

Primary Endpoint	Proportion of participants with disease extension (development of polyarthritis or uveitis) or need for systemic medication (s) for JIA (i.e. one or more of the following: systemic glucocorticoids, DMARD or biologic) within 12 months post-enrollment.
Secondary Endpoints	• PRO group differences including PROMIS® measures (pain interference, fatigue, upper extremity function, mobility, anxiety, depression, and global health) and medication side effects (JAMAR), CHAQ • Proportion of children achieving clinical inactive disease and/or remission • Number of new joints with arthritis • Cumulative number of glucocorticoid joint injections • Serious adverse events • Juvenile arthritis disease activity scores (JADAS) • Elapsed time from enrollment to disease extension, uveitis or systemic DMARD medication use • Proportion of participants with disease extension (development of polyarthritis or uveitis)
Study Schedule Definitions	• 6 months is equal to 24 weeks or 24 doses of abatacept • 12 months is equal to 48 weeks

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the investigator brochure, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make all reasonable efforts to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor. I will discuss this material with them to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted. I agree to adhere to the attached protocol.

I agree to provide all study participants with informed consent, as required by government regulations and International Conference on Harmonization guidance. I further agree to report to the sponsor any adverse experiences in accordance with the terms of this protocol.

_____

Principal Investigator Name (print)

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Signature

_____

Date

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ABBREVIATIONS

AE	Adverse Event
ACR	American College of Rheumatology
ALT (SGPT)	Alanine transaminase
AM	Ante Meridiem
ANA	Antinuclear Antibodies
ARCH CDRN	Accessible Research Commons for Health Clinical Data Research Network
AST (SGOT)	Aspartate aminotransferase
BMS	Bristol-Myers Squibb
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CBC	Complete Blood count
CCP	Cyclic citrullinated peptide
CDM	Common data model
CDRN	Clinical Data Research Network
CFR	Code of Federal Regulations
CHAQ	Childhood Health Assessment Questionnaire
DCRI	Duke Clinical Research Institute
dL	Deciliter
DMARD	Disease-modifying anti-rheumatic drug
eCRF	Electronic case report form
EDC	Electronic data capture
ESI	Events of special interest
EHR	Electronic health record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability Accountability Act
HIV	Human immunodeficiency virus
HLA-B27	Human leukocyte antigen B27
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Conference on Harmonization

ILAR	International League of Associations for Rheumatology
IND	Investigational new drug
ITT	Intention to treat
IRB	Institutional Review Board
IV	Intravenous
JADAS	Juvenile Arthritis Disease Activity Score
JAMAR	Juvenile Arthritis Multidimensional Assessment Report
JIA	Juvenile idiopathic arthritis
JDM	Juvenile dermatomycosis
MAR	Missing at random
MCAR	Missing completely at random
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
NP	Nurse practitioner
NSAIDs	Nonsteroidal anti-inflammatory drug
PCORnet	Patient-Centered Clinical Research Network
PDSA	Plan-Do-Study-Act
PH	Proportional hazards
PHI	Protected health information
PI	Principal Investigator
PPD	Purified Protein derivative
pPH	Pediatric pulmonary hypertension
PRO	Patient-reported outcome
PROMIS®	Patient Reported Outcomes Measurement Information System
RA	Rheumatoid arthritis
REB	Research Ethics Board
RF	Rheumatoid factor
SAC	Stakeholder Advisory Committee
SAE	Serious adverse event
SOC	Standard of care

SQ	Subcutaneous
SUN	Standardization of Uveitis Nomenclature for Reporting Clinical Data
TB	Tuberculosis
ULN	Upper limit of normal

1 INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous, incompletely understood collection of inflammatory arthritides of unknown etiology defined by age at onset prior to 16 years.[1] With a prevalence of approximately 1 per 1,000 children, and many clinical phenotypes, JIA is one of the most common chronic diseases of childhood. JIA often persists into adulthood causing significant morbidity and impairing quality-of-life.[2-16] More than 50% of children with JIA present with "limited" disease, defined as arthritis involving ≤ 4 cumulative joints and no uveitis.[17] Children with limited JIA may meet criteria for one of 4 separate categories of JIA defined by the International League of Associations for Rheumatology (ILAR): oligoarthritis, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis.[1] However, scant evidence supports differential treatment of children based upon ILAR categories, which are fraught with uncertainties and inconsistencies.[18-27] Basing treatment decisions upon the number of joints affected to date, in contrast to ILAR categories, was endorsed by the 2011 American College of Rheumatology (ACR) Recommendations for the Treatment of JIA and more closely reflects current clinical practice.[28, 29] Therefore, the Limit-JIA study focuses on all children presenting with arthritis of ≤ 4 joints without uveitis. For the purpose of this trial, this phenotype is termed "limited JIA". Irrespective of ILAR category, children with limited JIA may develop significant morbidity, with only a minority achieving clinically inactive disease 12-18 months after disease onset. [4, 8, 30-32]

Disease extension in limited JIA. Children initially presenting with limited JIA frequently experience disease, defined as the development of polyarthritis (≥ 5 joints) or anterior uveitis, Both polyarthritis and uveitis are associated with worse clinical outcomes, including increased long-term physical disability and disease activity levels compared to children who present with polyarthritis at the time of diagnosis.[2, 6, 33-42] Fifty percent or more of children with limited JIA develop extension of oligoarthritis to polyarthritis (defined as ≥ 5 joints), including more than 25% within 2 years of disease onset.[2, 30, 39, 43-45] Reported arthritis extension rates vary between studies, likely reflecting genetic and environmental variation and methodological differences in the inclusion and follow-up of study participants.[46] Of note, previous studies focused on the ILAR category of oligoarthritis and did not include enthesitis-related arthritis or psoriatic arthritis, which have considerably higher rates of arthritis extension.[43]

One factor likely contributing to disappointing clinical outcomes for children presenting with early, limited JIA is delayed initiation of effective disease modifying anti-rheumatic drugs (DMARDs) and/or biologics.[35, 47] The development of anterior uveitis is also an important manifestation of limited JIA and can lead to permanent ocular disabilities such as glaucoma, cataracts, and vision loss.[36-38] Approximately 20% of children with limited JIA develop anterior uveitis, most often within 2 years of arthritis onset.[2, 30, 48] The development and subsequent severity of uveitis are often independent of arthritis manifestations, i.e., children may develop uveitis without concomitant extension to polyarthritis and vice-versa.[49] Lastly, a number of children may have persistent, limited JIA but inadequate response to treatment with nonsteroidal anti-inflammatory drugs (NSAIDS) and intra-articular glucocorticoid injections, requiring ongoing systemic treatment with DMARDs or biologic agents, even without extension of arthritis or development of new uveitis.[50-52] We therefore seek to determine whether early treatment with a 24-week course of abatacept (Orencia) will delay, diminish, or prevent the important outcomes of polyarthritis or uveitis, or need for systemic DMARD or biologic use during the study period and longer-term follow-up in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

Rationale for costimulatory blockage treatment for JIA. Abatacept (Orencia) is an approved, standard of care treatment for adults with rheumatoid arthritis (RA; USA and Canada) and for children with

polyarticular JIA (USA [SQ and IV] and Canada [IV form only]). Abatacept (Orencia) selectively inhibits a costimulatory signal required for T-cell activation, which is hypothesized to be an early step in the development of inflammatory arthritis. The 50 mg, 87.5 mg and 125 mg, SQ doses are approved for use in pediatric patients in the United States, whereas the 125 mg SQ dose is the only form approved for use in Canada.

Clinical trials in adults with RA have established that early treatment with biologic agents and DMARDs, during a "window of opportunity," improves long-term outcomes and reduces future disability.[54-56] In particular, a randomized, double-blind trial in undifferentiated arthritis (very early RA) demonstrated that a 6-month course of abatacept (Orencia) delayed disease progression in the majority of participants.[57] Unpublished results from an recent study presented at the 2021 American College of Rheumatology Annual Meeting showed that a 6 month course of abatacept reversed subclinical arthritis in participants at high risk for RA. [57, 58, 67] While such data is currently limited to adult RA and not JIA, the results strongly support the study of abatacept (Orencia) as a preventative agent for extension of disease in limited JIA.

Use of Electronic Health Record (EHR) data to improve efficiency in identification of participants with early disease and generalizability of study results. In Limit-JIA, treatment success is hypothesized to be associated with early treatment of JIA, and it is important to screen potentially eligible participants within six months of initial diagnoses. The ability to screen a high percentage of new onset patients would improve both the efficiency of study conduct and the generalizability of study findings to a larger non-study population. A principal focus of this study, therefore, involves the development of new, informatics-based screening techniques and procedures to enhance the timeliness and representativeness of study participant enrollment. The use of machine learning techniques to analyze EHR data is a promising approach to accomplish this goal; for example, in a recent registry-based study of Pediatric Pulmonary Hypertension (pPH) conducted at Boston Children's Hospital, use of the pPH registry alone, when compared against EHR-assisted data analysis approaches, identified fewer than half of the pPH patients seen.[53] Therefore, incorporating EHR-based study participant identification to more rapidly and comprehensively screen potentially eligible, recently diagnosed patients is likely to maximize overall study enrollment, minimize ascertainment biases, and improve overall study cost-effectiveness and scalability.

Improving data completeness. Assessment and minimization of missing data relevant to the tested hypotheses is critical to reaching clinically and statistically meaningful results. Performing linkages between disparate data sources (e.g. EHR, registry, and patient reported outcome (PRO) data) is likely to provide valuable insight into measuring and remediating specific domains of missing data, particularly those that are readily available and accurate in the EHR.

Advanced cohort identification and data linkage activities will be undertaken at a subset of participating CARRA Registry sites that are also data partners in the Patient-Centered Clinical Research Network (PCORnet) Accessible Research Commons for Health Clinical Data Research Network (ARCH CDRN). We will leverage existing PCORnet Common Data Model (CDM) infrastructure at these sites to enhance study participant recruitment and improve data completeness in a scalable fashion. Using a 'computable phenotype' for limited JIA will allow participating sites to generate screening lists of potential study-eligible participants based on EHR data. We will also link data obtained directly from EHR data sources with conventionally collected CARRA Registry study data in order to support data completeness.

Improving trial recruitment and retention through patient and caregiver engagement in research. Barriers and facilitators to trial enrollment, identified by previous surveys, point to issues such as

burden of visit schedule and how the study participant is approached. Unfortunately, best practices aimed at overcoming barriers to screening, recruitment and retention of study participants, particularly children, early in disease course are lacking. Unique challenges recruiting children include the dynamics of obtaining parental consent, different conception of clinical equipoise, and logistics (missing work and school). A systematic review reported the most common motivating factors for parents were health benefit for their child, altruism, trust in research, and the relationship with the researcher. Most commonly reported reasons for not participating were fear of risks, distrust in research, logistics and disruption of daily life routines. Scant research examining trial recruitment has been performed in the JIA population and no studies have examined patients early in disease course. According to one of our patient investigators, "*Receiving a diagnosis of JIA was an overwhelming experience for our family. We had always associated arthritis with old people and never knew children could also have arthritis. If we were approached to participate in a research project at this time, we would have declined. On top of being overwhelmed and confused by the diagnosis, we had a preconceived notion that participating in research meant that we were allowing our child to be a lab rat.*" This illustrates not only the problem of study enrollment at diagnosis but also the human element underlying the problem. Improvement in clinical trial enrollment and retention, especially around the time of diagnosis, is likely to be critically dependent upon incorporating a deeper understanding of the patient's and family's state of mind into the recruitment process. We will therefore explore, develop, and implement innovative ethnographic approaches that have been well-established as effective in other domains to capture and quantify current knowledge gaps in the lived experience of newly diagnosed early JIA in context of research trial participation.

2 OBJECTIVES

2.1 Primary Objective

To evaluate the effectiveness of a 24-dose course of treatment with the T-cell co-stimulation inhibitor, abatacept (Orencia), plus usual care that may include NSAIDs and/or intra-articular glucocorticoids versus usual care as derived from the CARRA Registry database, to prevent disease extension (development of polyarthritis [defined as ≥ 5 joints with arthritis] or uveitis) or the need for further treatment with systemic medication(s) for JIA (i.e. one or more of the following: systemic glucocorticoids, DMARD or biologic) medication within 12 months of enrollment in children with recent-onset limited JIA.

Hypothesis 2.1: Early treatment with abatacept (Orencia) will reduce the proportion of children who develop polyarthritis or uveitis, or need further treatment with systemic medication(s) for JIA (i.e. one or more of the following: systemic glucocorticoids, DMARD or biologic) within 12 months, compared to usual care.

2.2 Secondary Objectives

2.2.1 To evaluate the tolerability of weekly SQ abatacept and compare participant and caregiver reported outcomes between the treatment arm and standard of care as documented in the CARRA Registry.

Hypothesis 2.2.1: Patient-Recorded Outcomes (PROs) will remain stable or show improvement at 6 and 12 months in enrolled patients.

Hypothesis 2.2.2: There will be statistically significant differences in (PROs) between the two treatment strategies that can inform future participants and providers in selecting optimal treatments.

2.2.2 To enhance identification of eligible study participants by leveraging the EHR (at selected US sites only).

We will develop and refine proactive EHR-based processes for identifying study participants with recently diagnosed, limited JIA. Collaborating with PCORnet Accessible Research Commons for Health (ARCH) CDRN study sites, we will incorporate PCORnet Common Data Model (CDM) EHR selection queries to continuously generate screening lists of study-eligible study participants and compare with enrollment rates at non-ARCH sites. As feasible, other sites may assist in further validating such EHR selection queries using conventional EHR-based reports

Hypothesis 2.2.2: Incorporation of EHR-based study participant identification methods into conventional screening processes will improve enrollment rates for recently diagnosed participants with early JIA.

2.2.3 To optimize data completeness by leveraging EHR data (at selected US sites only).

Relevant data elements from the EHR at participating ARCH CRDN sites will be linked and incorporated into the CARRA Registry data warehouse for assessment of missing data domains. Linkages will be performed in ongoing completeness-improvement cycles across participating ARCH CDRN study sites.

Hypothesis 2.2.3: Incorporation of EHR data will provide statistically meaningful improvements in data completeness.

2.2.4 To improve clinical trial recruitment and retention.

We will improve clinical trial recruitment and retention of study subjects early in their disease course by identifying barriers and developing improved resources and processes. The study will focus on the following four domains of interest:

1. Understanding of disease/treatment
2. Trust
3. Perceived value of research
4. Time and logistics

Hypothesis 2.2.4: Integration of design thinking methods and enhanced understanding of enrollment barriers will lead to improved enrollment and retention rates of participants in a clinical trial early in disease course.

3 STUDY PARTICIPANT SELECTION

3.1 Number of Study Participants

Up to 30 centers in the US and Canada will participate in the study to enroll approximately 89 study participants (80 evaluable patients).

3.2 Clinical Trial Inclusion Criteria

To be eligible for this trial, participants must meet all of the following criteria in order to be included in the study:

1. Age ≥ 2 years old and ≤16.5 years old
2. Clinical diagnosis of JIA by a pediatric rheumatologist within the past 6 months
3. Arthritis affecting ≤4 joints between disease onset and enrollment
4. Enrollment in the CARRA Registry
5. Participants of childbearing potential must agree to remain abstinent or agree to use an effective and medically acceptable form of birth control from the time of written or verbal assent to at least 66 days after taking the last dose of study drug.
6. Weight ≥50 kg (Canadian Sites only)

3.3 Clinical Trial Exclusion Criteria

The presence of any of the following will exclude a study participant from inclusion in the study:

1. Systemic JIA as defined by 2004 ILAR criteria[1]
2. Sacroiliitis (clinical or radiographic)
3. Inflammatory bowel disease (IBD)
4. History of psoriasis or currently active psoriasis
5. History of uveitis or currently active uveitis
6. Prior treatment with systemic medication(s) for JIA (e.g. one or more of the following: DMARD or biologic medication)
7. Current or previous (within 30 days of enrollment) treatment with systemic glucocorticoids (A short course of oral prednisone [≤ 14 days] is allowed)
8. History of active or chronic liver disease
9. Chronic or acute renal disorder
10. AST (SGOT), ALT (SGPT) or BUN ≥2 x ULN (upper limit of normal) or creatinine ≥1.5 mg/dL or any other laboratory abnormality considered by the examining physician to be clinically significant within 2 months of the enrollment visit
11. Presence of any medical or psychological condition or laboratory result which would make the participant, in the opinion of the investigator, unsuitable for the study

12. Participation in another concurrent clinical interventional study within 30 days of enrollment
13. Known positive human immunodeficiency virus (HIV)
14. Received a live virus vaccine within 1 month of the baseline visit
15. Current or prior positive Purified Protein Derivative (PPD) test or Quantiferon Gold TB
16. Pregnant, breast feeding, or planned breast feeding during the study duration
17. Planned transfer to non-participating pediatric rheumatology center or adult rheumatologist in the next 12 months
18. Active malignancy of any type or history of malignancy
19. Chronic or active infection or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 30 days or oral antibiotics within 14 days prior to screening
20. Primary language other than English or Spanish
21. Positive for Hepatitis B surface antigen or core antibody
22. <10 Kg in weight
23. If a potential subject has symptoms consistent with COVID-19 and/or known COVID-19 exposure at screening, it is recommended that the site follow CDC guidance regarding testing and quarantine requirements. The subject can be re-screened when there is no longer concern for active infection. A subject with a positive COVID -19 test may be re-screened.

3.4 Candidate Computable Phenotype Criteria (at selected US sites only)

1. Recent diagnosis codes including oligo-articular JIA as well as undifferentiated/unspecified JIA types only, AND
2. Participants age ≥2 years old and ≤16.5 years old, AND
3. Seen in pediatric rheumatology clinic with first inclusion criteria diagnosis code within the preceding 20 weeks OR scheduled for upcoming pediatric rheumatology clinic visit with prior diagnosis of any type of arthritis within the preceding 20 weeks, AND
4. None of the following prior medications: systemic glucocorticoids, DMARDs OR biologics, AND
5. No prior diagnosis codes for Inflammatory Bowel Disease (IBD), systemic-onset JIA, sacroiliitis or ankylosing spondylitis, psoriasis, or uveitis

3.5 Ethnography Criteria (at selected US sites only)

There are four research study participant populations:

1. Families who are asked to participate in the clinical trial (Limit-JIA)
    a. Inclusion: Parents/guardians of JIA participants ≥2 years old and ≤16.5 years of age at the time of diagnosis, who were asked to participate in Limit-JIA, regardless of decision to enroll or not in the Limit-JIA study
    b. Exclusion: Non-English speakers
2. Site primary investigators
    a. Inclusion: Primary site investigator for Limit-JIA
    b. Exclusion: Non –English Speakers

3. Study coordinators
    a. Inclusion: Coordinators participating in the Limit JIA trial
    b. Exclusion: Non-English Speakers
4. Clinicians
    a. Inclusion: Pediatric rheumatology providers e.g. Medical Doctors (MDs, DOs) and Nurse Practitioners (NPs) at participating sites who are recruiting for the Limit-JIA trial but are not the study coordinator or site primary investigator.
    b. Exclusion: Non-English Speakers

4 STUDY DESIGN

4.1 Overview of Study

The study treatment consists of an open label 24-dose course of weekly subcutaneous (SQ) abatacept (Orencia) plus usual care, versus usual care subject comparators from the CARRA Registry to prevent the development of polyarthritis or uveitis, or initiation of systemic glucocorticoid, DMARD, and/or biologic medication within 12 months of enrollment in children with recent-onset limited JIA. Patients enrolled in the CARRA Registry receiving usual care who meet Limit-JIA inclusion/exclusion criteria will constitute the comparator arm, providing the proportion of children that develop disease extension on usual care alone.

There are 6 study visits: screening, enrollment, approximately month 3 (M3 visit), month 6 (M6 visit), month 9 (M9 visit), and month 12 (M12 visit [end of study]). The screening visit may be combined with the enrollment visit if all procedures can be completed and participant qualifies for the study. Clinical trial visits may occur either in person or via telehealth except for the screening or enrollment visits. One of these visits must be conducted in the clinic. The month 12 end of study visit must also be conducted in the clinic.

In order to enhance study recruitment and timely enrollment, a subset of Limit-JIA US based clinical trial sites will incorporate enhanced cohort identification of potential study participants that incorporates EHR-based algorithms to predict the presence of limited JIA. Specifically, a 'computable phenotype' will be utilized to generate screening lists of potentially eligible, recently diagnosed limited JIA patients who may be considered for enrollment. These EHR-based screening lists will then be further reviewed by site staff for study eligibility.

Study participant identification and enrollment using enhanced screening will be compared to use of traditional screening methods alone at this subset of sites. In addition, at a subset of US based sites, all enrolled CARRA Registry participants with JIA will have registry data supplemented by selected EHR data elements, which will be linked by the site and made available in the CARRA Data Warehouse, enabling analyses of registry data completeness.

In order to gain a better understanding of barriers to recruitment, enrollment and retention, a subset of participating US based clinical trial sites will participate in a sub-study focused on the patient journey through the clinical trial. This sub-study will follow a quasi-experimental time-series cross-sectional study design with initial tools development followed by three rounds of alternating data collection and iterative tools development to identify barriers and develop improved resources and processes to improve trial recruitment and retention of study participants.

4.2 Treatment Arms

Limit-JIA is a prospective open-label clinical trial. Children diagnosed with limited JIA (≤ 4 active joints and no uveitis) in the previous 6 months will be treated with a 24-dose course of weekly SQ abatacept (Orencia) plus usual care that may include NSAIDs and/or intra-articular glucocorticoids followed by 6 months of usual care. Abatacept (Orencia) will be dosed using the weight-based SQ pediatric dosing provided in the package insert (Table 1 below).

Table 1: Study drug dosing

Study drug dose will be adjusted for weight changes during the duration of the study drug administration period.

Study Drug	Dose by Weight	Dosage Form	Route	Dosage Frequency	Administration
abatacept (Orencia)	10 kg to < 25 kg: 50 mg	Solution for injection in pre-filled syringe (50mg in 0.4mL)	SQ	Once weekly	US based clinical sites only
abatacept (Orencia)	≥25 kg to < 50 kg: 87.5 mg	Solution for injection in pre-filled syringe (87.5mg in 0.7mL)	SQ	Once weekly	US based clinical sites only
abatacept (Orencia)	≥50 kg: 125 mg	Solution for injection in pre-filled syringe (125mg in 1mL)	SQ	Once weekly	US and Canadian based clinical sites

4.3 Study Assessment

4.3.1 Schedule of Assessment

Table 2: Schedule of Assessments (All assessments except the ophthalmology exams and screening and enrollment visits may occur in person or via telehealth.)

	Screen Visit	**Enrollment Visit (Baseline) (≤45 days)**	**M3 (+/-2 weeks)**	**M6 (+/-2 weeks)**	**M9 (+/-2 weeks)**	**M12 End of Study[1] (+/-2 weeks)**	**Interim Visits[2]**
Inclusion/Exclusion Criteria	X	X					
Consent/Assent	X						
Demographic Information	X	X					
Enrollment	X[10]	X					
Past Medical Hx (per CARRA registry)	X						
Physical Exam	X	X	X	X	X	X	X
Active Joint Count	X	X	X	X	X	X	X
Concomitant Meds (per CARRA registry)	X	X	X	X	X	X	X
Study Drug Adherence			X	X			
Dose/Instructions		X					
Drug Dispensation		X[12]	X[12]				
Ophthalmology Exam[3]	X See Ophthalmology Assessment Table 3 below The 1st Dose of study drug cannot be administered until after the screening eye exam has confirmed no disease. The M12 End of Study eye exam can be done up to 4 weeks after the end of study visit.						
MyStudies App enrollment		X					
Physician Global		X	X	X	X	X	X
Parent Global		X	X	X	X	X	X
PROMIS® Measures[7]	X	X	X	X	X	X	X
CHAQ		X		X		X	X
JAMAR		X	X	X			X
Duration of Morning Stiffness (Patient Reported)	X	X	X	X	X	X	X
JADAS		X	X	X	X	X	X
SAEs & ESIs (Per CARRA registry)	X	X	X	X	X	X	X
Quantiferon Gold/TB screen (drug can be administered in the absence of test results. Patient families will be instructed to not administer drug until a	X	X[11]					

	Screen Visit	Enrollment Visit (Baseline) (≤45 days)	M3 (+/-2 weeks)	M6 (+/-2 weeks)	M9 (+/-2 weeks)	M12 End of Study[1] (+/-2 weeks)	Interim Visits[2]
negative result is confirmed)							
Urine pregnancy screen[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
CBC	X[5]		X[4]	X[4]			
HBsAg[9]	X						
CMP	X[5]		X[4]	X[4]			
ESR/CRP[4]	X[4]		X[4]	X[4]	X[4]	X[4]	
ANA	X[6]						
HLA-B27, RF, anti-CCP (Per CARRA Registry)	X						
Covid-19 Survey[13]	**The patient/guardian will complete the Covid 19 Survey using the MyStudies App every week before study drug administration.**						

[1] End of study visit should be conducted at the end of the follow up period or if the participant discontinues the study for any reason, including development of polyarticular JIA or anterior uveitis, escape from treatment arm, safety concern, or withdrawal of consent.
[2] Interim visits occur whenever a study participant is evaluated clinically outside of the regularly scheduled study visit schedule for symptoms concerning for active arthritis, new anterior uveitis, or SAEs.
[3] Baseline Ophthalmology exam may occur at any time between the screening visit and the enrollment visit, including on the day of the screening visit or the enrollment visit. Prior baseline exam will be accepted if done within 45 days of enrollment.
[4] Only if obtained as SOC. Not required specifically for study.
[5] Screening CBC and CMP must be obtained within 2 months prior to enrollment. If not available or abnormal from previous SOC labs, CBC and CMP must be obtained prior to enrollment.
[6] ANA results required prior to enrollment.
[7] See Table 5 for specific instructions.
[8] For females with childbearing potential and should be repeated at any time during study duration per standard of care by participant's provider.
[9]Subjects who have not been screened for Hepatitis B as part of SOC will get one as part of screening or enrollment. Study drug can be dispensed prior to obtaining study results. Patient families will be instructed to not administer drug until a negative result is confirmed. If test results are positive, the subject will be discontinued from the study.
[10]Enrollment may occur during screening visits or at a separate specific enrollment visit.
[11]Subjects who did not have a Quantiferon Gold or TB test as part of SOC will get one as part of screening or enrollment. Study drug cannot be administered in the absence of a negative test result.
[12]A 3- or 6-month supply of abatacept will be provided at the enrollment visit. Re-supply will occur at M3 if a 3-month supply was provided at enrollment.

4.3.2 Explanation of Assessments

- **Informed consent and assent** (if applicable)**:** Obtained prior to any study related procedure.

- **Telehealth:** The provision of healthcare remotely by means of telecommunications technology.

- **Screening:** Screening is defined as having signed consent to participate in the Limit-JIA study.

- **Enrollment :** May occur at the time of screening visit if all required data are available or up to 45 days after obtaining consent.

- **Demographic Information:** Relevant subject information that includes date of collection, date of birth, age, gender and ethnicity.

- **Past Medical History:** Relevant JIA history, including date of onset of symptoms, date of diagnosis, specific joints ever affected. Relevant comorbid conditions.

- **Physical Exam:** Basic examination of organ systems other than musculoskeletal, including vital signs with temperature.

- **Active Joint Count:** Active arthritis is defined as joints with swelling not due to bony enlargement or joints with limitation of motion accompanied by either pain on motion and/or tenderness. For the purposes of counting affected joints, each toe counts as a single joint irrespective of whether it is the proximal interphalangeal joint (PIP), the distal interphalangeal joint (DIP), or both that are affected, consistent with previous clinical trials conducted in JIA. Participants must have a diagnosis of limited JIA by a pediatric rheumatologist. Patients do not need an active joint at time of enrollment to be eligible for the study. A patient who has been treated with systemic medication(s) is no longer eligible for the study.

- **Duration of Morning Stiffness:** Assessment of the duration of soreness and restricted movement upon awakening. This is a patient reported parameter.

- **COVID-19 Survey**- Assessment of COVID-19 symptoms via MyStudies App or paper.

- **Concomitant Medications:** Record all medications taken for treatment of study disease taken more than a year prior to Baseline, please complete as much information as possible, including best estimate of at least the year of start and stop. Please complete a new log line each time a dose is changed.

- **Study Drug Adherence:** Family report of administration of SQ abatacept (Orencia) via medication adherence diary (MyStudies App or paper diary).

- **Physician Global:** Physician Global Assessment of disease activity on 21-point scale from 0 to 10 in increments of 0.5

- **Patient Reported Outcomes Measurement Information System (PROMIS®) & other PRO Measures Appendix A):** PROMIS® fatigue, mobility, upper extremity function, pain interference, anxiety, depression, and global health measures will be administered via tablet or paper short-forms to the participant and/or guardian per CARRA Registry protocols. Other PROs collected are the Parent Global Assessment of overall wellbeing (11-point scale, 0 to 10 in increments of 1) and the Childhood Health Assessment Questionnaire (CHAQ). JAMAR, Covid Survey. Refer to Appendix for assessment details.

- **Serious Adverse Events (SAEs):** Occurrence of any serious adverse events from time of informed consent.

- **Events of Special Interest (ESIs)**: Protocol-defined adverse events of special interest will be collected from time of informed consent. Refer to 7.5.

- **TB screen:** Participants can be screened by either Quantiferon Gold assay or PPD per the treating physician. If a Quantiferon Gold or PPD has been performed within the prior 6 months and is negative, it need not be repeated at screening, unless the participant has changed from low to high risk. Subjects may be enrolled before PPD or Quantiferon Gold assay TB results are reported**.** Subjects who did not have a Quantiferon Gold or PPD as part of SOC will get one as part of screening or enrollment. However, study drug can be dispensed prior to obtaining study results. Patient families will be instructed not to administer drug until a negative result is confirmed. If test results are positive, the subject will be discontinued from the study.

- **Urine pregnancy screen**: Menstruating females must have a negative urine pregnancy test at enrollment and for the duration of the trial. The test may be repeated at any time during study duration per standard of care by participant's provider.

- **Laboratory Assessments**

    - **ANA**
        - ANA results drawn at or after diagnosis of JIA may be used.
        - ANA results are required prior to enrollment.

    - **HLA-B27, RF, CCP:**
        - If these were obtained during initial evaluation for JIA, they do not need to be repeated.
        - Results are not required prior to enrollment and are not part of the study eligibility criteria.

    - **CBC/CMP :**
        - Screening CBC (hemoglobin, platelets and white blood cell count) and CMP (ASP/ALT/Creatinine) must be obtained within 2 months prior to enrollment. If not available or abnormal from previous SOC labs, CBC and CMP must be obtained prior to enrollment.
        - Month 3/6: Only if obtained as SOC. Not required specifically for study.

    - **ESR/CRP**:
        - Results not needed prior to enrollment. Results will be captured at each study visit if obtained as part of SOC; however, not required as part of the Limit-JIA study

    - **Hepatitis B**

- All patients receiving abatacept should be screened clinically and undergo serologic testing if indicated for viral hepatitis prior to use as anti-rheumatic therapy may cause reactivation of hepatitis B.
- Subjects who have not been screened for Hepatitis B as part of SOC will get one as part of enrollment. Study drug can be dispensed prior to obtaining study results. Patient families will be instructed to not administer drug until a negative result is confirmed. If test results are positive, the subject will be discontinued from the study.

4.3.3 Recommended Ophthalmology Assessments

The frequency of ophthalmology assessment for each participant depends on the presence or absence of known risk factors for JIA associated uveitis including ANA status and age at onset of JIA as per Table 3 below. Per protocol, a screening ophthalmology exam is *required within 45 days prior to* enrollment. A subject may complete the rheumatology screening visit and then have the screening ophthalmology exam performed after enrollment. In this case, **the 1st Dose of study drug cannot be administered until after the screening eye exam has confirmed no uveitis.**

The Month 12 (end of study) eye exam is also *required; however, it can be obtained up to 4 weeks after the end of study visit.*

The presence of active anterior uveitis will be defined according to the Standardization of Uveitis Nomenclature for Reporting Clinical Data (SUN criteria)[62]: the presence of 1 or more cells in each 1mm x 1mm slit beam field (Grade 0.5+ or trace cells). During the study, evaluation for anterior uveitis follow SOC intervals described by the Heiligenhaus modification of the American Academy of Pediatrics recommendations[63].

Table 3: Recommended Schedule of Ophthalmology Exam

	ANA	Age at JIA Onset	Screen Visit**	M 3	M 6	M 9	M 12***
Oligoarthritis* (Q3 months)	+	≤ 6	X	X	X	X	X
Oligoarthritis* (Q6 months)	+	> 6	X		X		X
Oligoarthritis* (Q6 months)	–	≤ 6	X		X		X
Oligoarthritis* (Q12 months)	–	> 6	X				X
Enthesitis-related arthritis	+ or –	Any	X				X

*Includes ILAR categories of oligoarthritis, psoriatic arthritis (if no current active psoriasis or history of psoriasis), and undifferentiated arthritis.
** Screening ophthalmology exam required within 45 days of enrollment.
*** Month 12 screening required within 4 weeks of End of Study visit.

4.4 Screening and Pre-Enrollment Procedures

All eligible study participants will be recruited from CARRA Registry sites.

All participants are also consented and enrolled in the CARRA Registry and will have a CARRA Global ID number. Additionally, study participants will be assigned a Limit-JIA study participant number at the time the consent is signed.

For the purpose of this study the term enrolled will be defined as having signed consent. Children with limited JIA who have provided assent if required and whose parent/legal guardians have given written permission will be screened for Limit-JIA. If they meet all inclusion and no exclusion criteria, they will be enrolled into the study. They will concurrently consent and enroll into the CARRA Registry protocol (if not already enrolled in the CARRA Registry). Written or electronic informed consent will be obtained per each enrolling site's or the central IRB's requirements.

4.5 Screen Failure

Any participant who completes the screening visit, but is subsequently found to be ineligible for the study (e.g lab test results out of range/positive) will be a screen failure.

If a subject is started on systemic DMARDS, biologics, or systemic glucocorticoids between screening and enrollment then this subject will also be considered a screen failure.

4.6 Screening Visit (either the screening visit or enrollment visit must be in person to confirm the diagnosis)

Research staff will document informed consent from the parent/guardian, and if applicable, child assent according to local regulations for all study participants who satisfy eligibility criteria. The following information will be recorded in the CRF:

1. Consent/Assent
2. Past medical history
3. Physical examination
4. Joint exam – active joint count
5. Concomitant medications
6. TB screening
7. Hepatitis screening (if indicated)
8. CBC
9. CMP
10. ESR/CRP (only if obtained as SOC)
11. ANA

12. HLA-B27, RF, CCP (if obtained as SOC)
13. Ophthalmology Exam
14. Urine Pregnancy Test if indicated

4.7 Enrollment Visit (Within 45 days after Screening Visit; may be combined with the Screening visit)

1. Review of Inclusion/Exclusion criteria to be performed prior to enrollment
2. Physical examination
3. Joint Exam - Active joint count
4. Interval history - If enrollment occurs at a different visit than screening. Interval history to include interval use of systemic DMARDS, NSAIDs, biologics and intra-articular glucocorticoid injections, new co-morbid conditions, any encounters with health care professionals.
5. Concomitant medications
6. Results of urine pregnancy screen
7. Enrollment in MyStudies App
8. SAE & ESI review and reporting
9. Physician Global Assessment
10. Parent Global Assessment
11. PROMIS® measures – See Table 5
12. CHAQ
13. Juvenile Arthritis Multidimensional Assessment Report (JAMAR)
14. Juvenile Arthritis Disease Activity Score (JADAS)
15. Drug Dispensation (a 3 month or a 6 month supply can be provided)
16. Dose Instructions/Administration
17. Ophthalmology Exam (if not available at screening)

4.8 Post Enrollment Procedures (Month 3 to Month 12; in person or via telehealth) Month 3/Month 6 (+/- 2 weeks; in person or via telehealth)

1. Physical examination
2. Joint Exam - Active joint count
3. Interval history to include interval use of NSAIDs and intra-articular glucocorticoid injections, new co-morbid conditions (including psoriasis), encounters with health care professionals (specifically in response to uveitis, active arthritis, or serious adverse events).
4. Drug dispensation (Month 3 only – re-supply, only if a 3 month supply was provided at Baseline)
5. Drug adherence
6. Ophthalmology exam per Table 3
7. Concomitant Medications
8. Physician Global Assessment
9. Parent Global Assessment
10. Selected PROMIS® measures – See Table 5
11. CHAQ (6 month only)
12. JAMAR
13. JADAS
14. SAEs

15. ESIs
16. ESR/CRP/ CBM/ CMP (Only if obtained as SOC)
17. Data entry of SOC labs if available
18. Results of urine pregnancy screen -May be repeated at any time during study duration per standard of care by participant's provider.

Month 9/ (+/- 2 weeks; in person or via telehealth)

1. Physical Examination
2. Joint Exam - active joint count
3. Interval history to include interval use of NSAIDs and intra-articular glucocorticoid injections, new co-morbid conditions (including psoriasis), encounters with health care professionals (specifically in response to uveitis, active arthritis, or serious adverse events).
4. Concomitant medications
5. Ophthalmology exam per Table 3
6. Physician Global Assessment
7. Parent Global Assessment
8. Selected PROMIS® measures – See Table 5
9. JADAS
10. SAEs
11. ESIs
12. ESR/CRP/CBC/CMP (Only if obtained as SOC)
13. Data entry of SOC labs if available

Month 12 End of Study Visit (+/- 2 weeks; in person only)

1. Physical examination
2. Joint Exam - active joint count
3. Interval history to include interval use of NSAIDs and intra-articular glucocorticoid injections, new co-morbid conditions (including psoriasis), with health care professionals (specifically if related to uveitis, active arthritis, or serious adverse events).
4. Concomitant medications
5. Ophthalmology exam per Table 3
   - Ophthalmology exam may be up to 4 weeks after the Month 12 visit
   - Record results if performed as part of standard of care.
6. Physician Global Assessment
7. Parent Global Assessment
8. Selected PROMIS® measures – see Table 5
9. CHAQ
10. JADAS
11. SAEs
12. ESIs
13. ESR/CRP/ CBC/ CMP (Only if obtained as SOC)
14. Data entry of SOC labs if available

Interim Visit (in person or via telehealth)

1. Physical examination
2. Joint Exam - Active joint count
3. Interval history to include interval use of NSAIDs and intra-articular glucocorticoid injections, new co-morbid conditions (including psoriasis), encounters with health care professionals (specifically in response to uveitis, active arthritis, or serious adverse events).
4. Concomitant Medications
5. Drug Adherence (If subject is currently taking study drug at time of interim visit)
6. Ophthalmology exam
7. Physician Global Assessment
8. Parent Global Assessment
9. Selected PROMIS® measures – see Table 5
10. CHAQ
11. JAMAR
12. JADAS
13. SAEs
14. ESIs
15. ESR/CRP/ CBC/ CMP (Only if obtained as SOC)

4.9 Immunizations

- No live vaccines administered within one month of enrollment.
- Live vaccines are prohibited during abatacept administration and for three (3) months after administration of the last abatacept dose.
- With regards to vaccinations for COVID-19, the guidance set forth by the American College of Rheumatology should be followed. Refer to the COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force. Version 4 from August 19, 2021 states that the abatacept dose should be held both one week prior and one week after the first COVID-19 vaccine dose (only). There should be no interruption around the second vaccine dose.[68]

4.10 Development and Utilization of EHR based Algorithms for Enhanced Study Recruitment at Subset of Trial Sites (US Based Sites Only)

The comprehensive and timely screening of all potentially eligible study participants is an important determinant of study success for Limit-JIA. An aim of this study is therefore the development and utilization of algorithms and processes employing Electronic Health Record (EHR) data for such cohort screening. The development of such algorithms has previously been utilized for other pediatric chronic diseases (e.g. pediatric pulmonary hypertension) by the Accessible Research Commons for Health Clinical Data Research Network (ARCH CDRN); this approach will be further developed to enhance recruitment for Limit-JIA.

A subset of Limit-JIA study sites that also participate in the ARCH CDRN, as well as other Limit -JIA sites wishing to participate in this phase of the study, will (1) execute cohort

definition queries against their site's local clinical research data warehouse, resulting in the generation of a list of potentially eligible study participants, and (2) perform manual chart review on the list of their site's potentially eligible subjects, resulting in a refined list of potentially study-eligible subjects who may subsequently be approached for study participation according to usual, IRB-approved mechanisms for doing so at each individual Limit-JIA study site.

These initial cohort definition queries and chart review activities will undergo iterative refinement to develop progressively more responsive sets of classifiers (a "computable phenotype") that optimally balances sensitivity vs specificity regarding subject study eligibility. As part of this process, sites participating in development of the computable phenotype will develop a 'gold standard' list of patients known to have limited JIA ('positive' cases) and patients known to not have limited JIA ('negative' cases). These activities will consist of EHR data set analyses and chart review activities only. The data sets generated for this purpose will not be used for subject recruitment or enrollment, although subjects included in the computable phenotype validation cohort may be enrolled in Limit-JIA and/or the CARRA Registry but will not have been identified for enrollment via this process. We estimate that up to 100 individuals per group (positive and negative cases) per site will be identified, with positive cases identified via available methods (e.g. using a validated list from chronic disease registries, billing records, etc., which may vary at each site). The negative case group will consist of individuals matched to possess similar characteristics, e.g. age and gender, but who do not have limited JIA. Identification of these case groups will be accomplished via queries of a site's clinical data warehouse and using chart review.

4.11 Abstraction and Linkage of EHR Data and CARRA Registry Data for Assessment and Improvement of Data Completeness (US Based Sites Only)

Data that is manually abstracted from the EHR and expressly collected for registry and other clinical studies represents a 'gold-standard' that is typically difficult, if not impossible, to obtain at the same level of fidelity via automated extraction from EHR data warehouses. However, manual data abstraction is much more costly and difficult to accomplish than automated processes of mining EHR data that obtain lower-fidelity data. For this study, we therefore employ a hybrid approach for a sub set of sites in which a core of manually curated study data will be augmented by linkage with a subject's selected EHR data elements. Categories of EHR data elements to be collected include demographics, dates of encounters, diagnoses, problem lists, family history, social history, procedures, medications, laboratory data, radiology data, physician specialties, patient-reported outcomes, and related information.

At the subset of sites participating in EHR data abstraction and linkage, EHR data elements for participants enrolled in this study, as well as other subjects with JIA enrolled in the larger CARRA Registry, will undergo linkage to Limit-JIA and CARRA Registry data using site medical record numbers and the corresponding mappings to CARRA Registry unique subject identifiers. Each participating site will then compose a limited data set of selected EHR data elements using the CARRA Registry subject identifier for each consented participant as a coded identifier. This data set will then be securely transferred to the CARRA Data Warehouse. The combined study, registry, and EHR data will be made available to study investigators and analysts enabling estimation of registry data completeness (see Analysis Plan, Section 8.3, and "Major Secondary Analyses").

4.12 Ethnography Study Design (US Based Sites Only)

The ethnography sub-study will follow a *quasi-experimental, time-series cross-sectional study design* with up to three observations and iterative design occurring between each step. The aim of this sub-study at select US sites is to improve clinical trial recruitment and retention of study participants by identifying barriers and developing improved resources and process. The coordinating center for the sub study is LIFT. The sub study activities are covered by a separate IRB approval and protocol managed by LIFT.

4.12.1 Patient/Family Recruitment & Enrollment Process

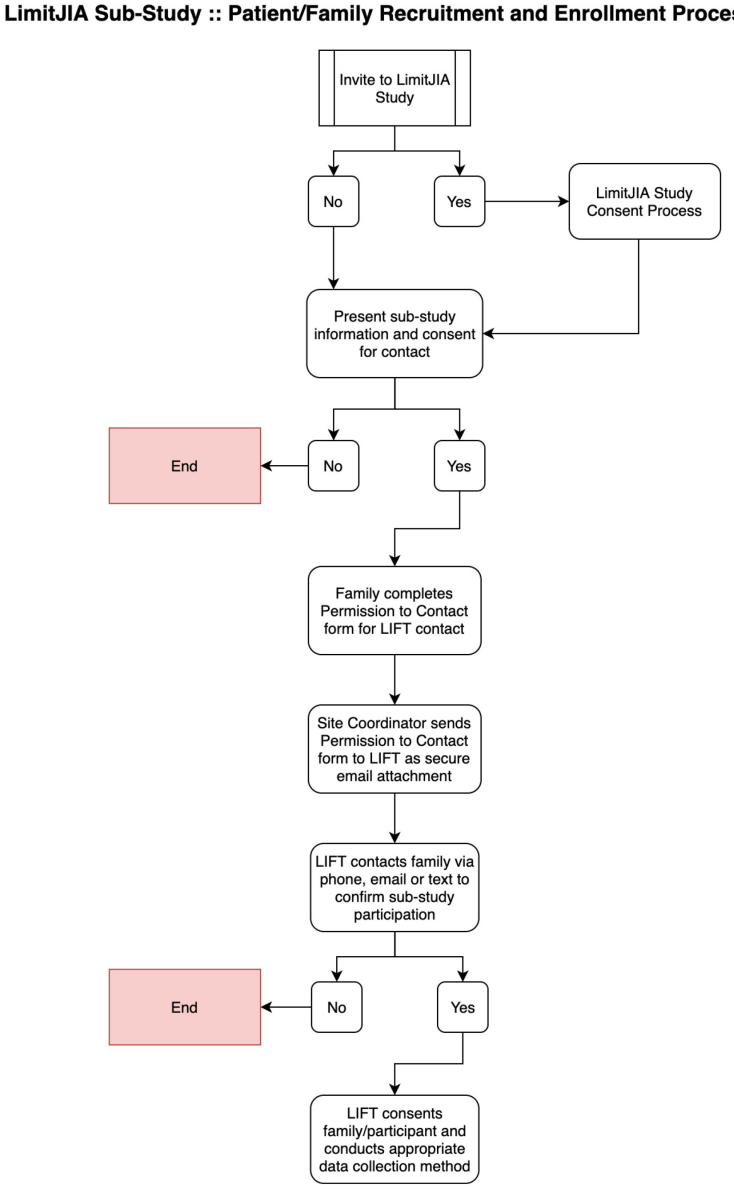

Figure 1: Flowchart of study participant/family recruitment and enrollment process.

1. Families who meet the inclusion criteria for Limit-JIA will be asked by the site study team to participate in the main Limit-JIA study.
2. After completing the main Limit-JIA consent process, regardless of whether the family decides to participate in the main study, families will be presented

information about the ethnography sub study along with two copies of a Permission to Contact form for them to sign providing permission for them to be contacted by LIFT, the sub study-coordinating center.

3. Families who agree to be contacted will complete and sign the contact permission form, leaving one copy for the site study team and keeping the other for their own records.
4. The site coordinator contacts LIFT within 48 hours via secure email provides a copy of the permission to contact form to the LIFT study manager, which includes the study participant name, parent/family member name, email, and telephone number.
5. The LIFT study manager contacts families who have agreed to be contacted to provide additional information about the sub-study, address any questions, and schedule the interview.
6. The LIFT study manager and/or researcher will consent the family/participants at the time of the interview and complete the appropriate study components (e-survey, telephone survey, in-home immersion).

4.12.2 Staff Recruitment & Enrollment Process

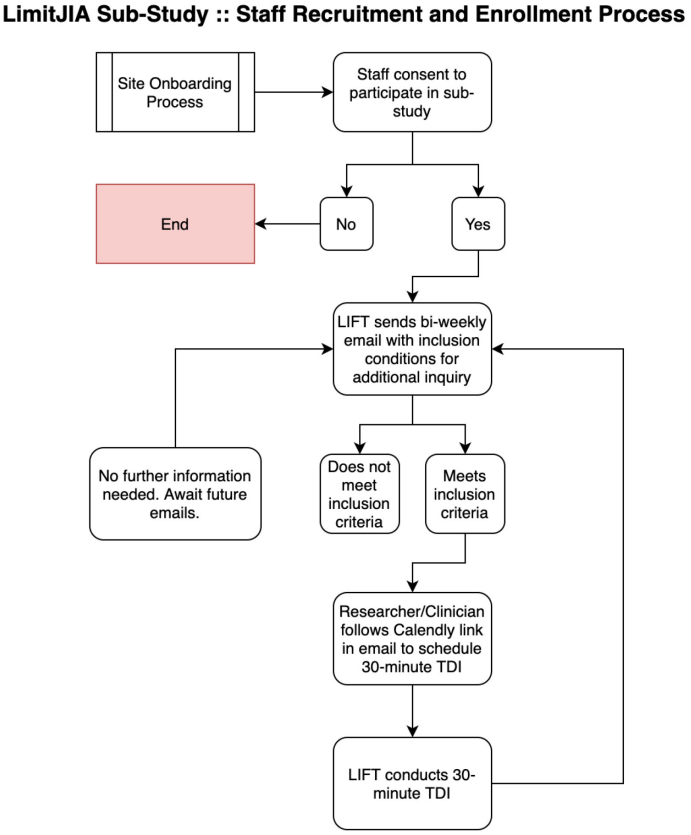

Figure 2: Flowchart of staff recruitment and enrollment process.

1. During site activation, all associated site staff members (clinicians, site investigators, and study coordinators) will receive information and an email containing a digital consent forms for participation in the sub-study.
2. Study staff will receive bi-weekly emails asking if they have screened an eligible Limit-JIA patient in the past week. Study staff that have seen an eligible Limit-JIA patient will follow a Calendly® link to schedule a 30-minute telephone interview, to take place within the next 10 business days. Study staff that have not seen an eligible Limit-JIA patient will receive no additional inquiry for this study week but will be included in all future email requests for information.
3. LIFT study manager will coordinate with site staff to collect appropriate data based on the study sample.
4. Repeat steps 2 through 3 for the duration of the study cycle.

4.12.3 Sites

Limit-JIA will be conducted at approximately 40 sites. This sub-study will be conducted at a subset of US based sites.

4.12.4 Ethnography Assessments and Study Timeline

In addition to collecting information about the patient/family experience the following information will be collected about each patient: age, gender, race/ethnicity. The participant will have the option to decline providing this information.

4.12.5 Initial Design of Materials (US Based Sites Only)

Version 1 of the recruitment and retention materials will be prepared in consultation with the Stakeholder Advisory Committee (SAC) and the Design Process Improvement Group (DIG). Both groups include parents, participants, payers, and site coordinators, using examples from prior LIFT studies. Recruitment to the Limit-JIA trial will begin with V1 of the recruitment materials.

4.12.6 Ongoing PDSA and Tools Improvement (US Based Sites Only)

PDSA cycles will be used to improve recruitment and retention materials and messaging for the Limit-JIA trial. Virtual immersions and telephone interviews will be used during the PDSA cycles of the study. Transition from each observation phase to the design phase will occur when saturation has been achieved. The number of PDSA cycles necessary will be determined based on the level of saturation during each data collection phase and the pace of participant enrollment. Feedback from participants will be incorporated to improve the recruitment materials at each cycle. The DIG, an extension of the Limit-JIA SAC for the ethnography study, provides design input and oversight over tools improvement.

5 MYSTUDIES APP

5.1 Description of the MyStudies Mobile App

The FDA MyStudies App is designed to facilitate the input of real world data directly by patients which can be linked to electronic health data supporting traditional clinical trials, pragmatic trials, observational studies and registries. This platform has been developed under sponsorship of the FDA and private sector partners as open source software, enabling the app and associated data storage to be configured by organizations conducting clinical research according to their needs and utilizing their own branding.

All users of the MyStudies Mobile App will be asked to register for the app using a unique email address. The email address is used to confirm that the registrant is a real person. The user will receive a confirmation email with a confirmation code. The user will not be officially registered in the app until they enter the code in the app. This registration code is distinct from a patient token, which each subject will be provided by study staff for use in enrolling in the study. All users must consent to a study before completing any study surveys. The site maintains control of the release of patient tokens for the app and will only release them once the consent to participate has been signed by the parent/legal guardian.

Study participants may be alerted to new surveys by "push notifications." A notification will pop up on their smart phone screen, telling them a new survey is available. Participants will be able to turn off notifications of new surveys at any time. The use of push notifications does not require any personal identifiers, such as a cell phone number.

5.2 Data Access Security and Storage

Data collected by the MyStudies mobile app will be transferred to and stored with the project vendor/collaborator LabKey.

All personal health information collected and stored on the LabKey platform for this study will be deleted from that platform within 60 days of completion of study data analysis, unless such data collection and usage subsequently becomes governed by another IRB-approved protocol, such as for the CARRA Registry.

Harvard Pilgrim Health Care Institute (HPHCI, the coordinating center for MyStudies mobile app, will use the platform hosted by LabKey Software, to provide a set of unique patient enrollment tokens for distribution to the study cohort. HPHCI will distribute these tokens to study site personnel, and study site personnel will assign and distribute a token to each participant as they identify and enroll them in the study cohort. Study personnel will maintain the linkage of token associations with participant identifiers.

Participants respond to questionnaires in the MyStudies mobile app at their convenience for as long they are available in the app. Data are stored locally on the app until the participant indicates they have completed the questionnaire or task by tapping "done" on the final screen. Data will be encrypted during transmission and in the LabKey Server. Participants can optionally use a Passcode/TouchID/FaceID (depending on phone capabilities) to prevent others who may be using their phone from accessing the MyStudies app.

Only designated staff at HPHCI will have access to patient-reported data captured by the MyStudies mobile app and housed within the LabKey platform. Designated CARRA Registry staff will have access to view and download MyStudies subject data, including individual-level data, and link individual-level data with other CARRA Registry data using MyStudies and CARRA Registry subject identifiers. The HPHCI designated staff may create data queries, review aggregated query results, and view individual-level data without otherwise downloading patient data.

5.3 Survey Distribution for Mobile App Users

Surveys will be distributed to app users who have consented to the study on the following schedule:

- **Study Arm 1 (Intervention group)**
  - One question survey asking on what date the medication was last administered.
    - Schedule: Available immediately after enrollment in the study in the app
    - Duration: Available until completed by the patient
    - Other notes:
      - The response to this question will be used as the **anchor date** for the medication administration survey
  - Covid-19 Survey
    - Schedule: Weekly, starting on **anchor date** + 1 week
    - Duration: Available for 12 months (48 weeks) based on enrollment date of patient in the app
  - Medication Administration Survey
    - Schedule: Weekly, starting on **anchor date** + 1 week
    - Duration: Available for 48weeks post enrollment
  - Uveitis Survey
    - Schedule: Available continuously
    - Duration: Available for 12 months (48 weeks) based on enrollment date of patient in the app
    - Other notes:
      - Appointment dates do not need to be entered in the app.
      -

5.4 Survey Notifications

Participants may receive the following phone notifications when using the app to participate in this study.

- A new activity is available/an activity is about to expire
  - Text: A new run of the scheduled activity <activity name>, is now available and is valid until <Month, DD, YYYY TT>. Your participation is important. Please visit the study to complete it now.
- A one-time activity is starting
  - Text: The activity <activity name>, is now available to take. Please visit the study to complete it.

- New run of weekly/monthly existing activity
    - Text: A new run of the <weekly/monthly/ > activity <activity name>, is now available. Please visit the study to complete it.
- Weekly activity is set to expire
    - Text: The current run of the weekly activity <activity name>, will expire in 24 hours. Your participation is important. Please visit the study to complete it now.
- The study is paused via the WCP
    - Text: The study <study name > has been paused We will notify you when it is resumed.
- The study is resumed via the WCP
    - Text: The study <study name as given in WCP 50 char max> has been resumed. Visit the study to start participating in activities again.
- The study is close the study via the WCP
    - Text: The study <study name > has been closed. We thank you for your participation.
- A new resource has been added
    - Text: custom

6 CLINICAL TRIAL TREATMENT INTERVENTIONS

All eligible participants will be enrolled to receive treatment with 24-doses of weekly SQ abatacept (Orencia) plus usual care.

6.1 Abatacept (Orencia) – Study Drug

Participants enrolled to receive SQ abatacept (Orencia) will receive training and study materials (3 month or 6 month drug supply) on the day of enrollment. The first dose should be administered at the site or at home with telehealth guidance from the investigator or other study staff once all test results have been verified. All study participants enrolled will be trained by the study staff on study drug administration. A resupply of IP will occur at the three-month visit if a 6-month supply was not provided at enrollment.

The 50 mg, 87.5 mg and 125 mg SQ doses that are approved for use in pediatric patients in the United States will be supplied by a US-based depot. The 125 mg SQ dose approved for use in Canada will be sourced from a Canadian vendor.

6.2 Potential Benefits/Risks of Abatacept (Orencia)

The safety profile of abatacept (Orencia) is well-established, with infection (primarily upper respiratory tract) and injection site reactions most common.[59, 60]

6.3 Storage

Study drug solution supplied in prefilled syringe should be refrigerated at 2°C to 8°C (36°F to 46°F). Do not use study drug beyond the expiration date on the prefilled syringe. Protect from light by storing in the original package until time of use. Do not allow the prefilled syringe to freeze.

6.4 Study Drug Discontinuation Criteria

Study participants who permanently stop study drug in Limit-JIA should be encouraged to continue in the study. If for any reason a study participant must permanently stop study drug, every effort should be made by the Site Investigator/staff to keep the study participant in the Limit-JIA study to collect important safety and clinical data.

Withdrawal from the Limit-JIA study does not automatically withdraw the study participant from the CARRA Registry.

Study participant must be permanently discontinued from the study drug if the following occurs:

- Positive urine pregnancy test

- Non-compliance with study drug. Study participants' compliance with study treatment will be assessed throughout the study. Participants who miss more than one dose should be re-educated on the requirement for treatment compliance. Every effort will be made to keep participants in the study and to re-educate those who continue to miss doses. Participants who continue to be non-compliant after multiple visit assessments may be permanently discontinued from study drug at the discretion of the Site Investigator after consultation with the sponsor.

- Non-compliance with weekly diary. Study participants' must complete their weekly electronic or paper diary between study visits. Participants who are non-compliant after multiple visit assessments may be permanently discontinued from study drug at the discretion of the Site Investigator after consultation with the sponsor.

- Serious Infection

- Physician discretion

- Achievement of any of the primary outcomes as defined in the protocol (disease extension, uveitis and/or need for escalation of systemic therapies)

- SAE attributed to abatacept

- AE attributed to abatacept that at the discretion of the site PI warrants drug discontinuation.

- Conversion to positive PPD or Quantiferon Gold assay result that occurs during the study (if tested as standard of care)

6.4.1 Procedures for Monitoring Study Drug Compliance

The participant/parent will be given a patient diary (electronic app or paper diary) and will be instructed how and when to use the study drug. The study participant diary will be reviewed at each visit throughout the study to confirm the study participants' compliance with study drug throughout the study. Participants who are non-compliant should be re-educated on the importance of treatment compliance

6.4.2 Temporary Discontinuation of Study Drug

Abatacept can be temporarily held for a maximum of 2 weeks for significant viral infections or for bacterial infections requiring antibiotics. Patients may continue/resume study drug at discretion of physician. Temporary discontinuation of study drug for COVID-19 infection should be handled the same as temporary discontinuations for other viral infections. Study drug administration in COVID-19 positive patients will be handled per physician discretion, following CDC and American College of Rheumatology COVID-19 guidelines. With regards to vaccinations for COVID-19, administration of abatacept will follow the guidance set forth by the American College of Rheumatology to hold SQ abatacept one week prior and one week after the first COVID-19 vaccine dose (only). There is no interruption around the second vaccine dose.[68]

6.4.3 Discontinuation of Study Drug

Study participants may choose to stop taking study drug before the end of the study. A participant may also be asked to stop study drug at the Site Investigator's discretion. Participants who have permanently discontinued study drug are not required to withdraw from the study. Participants who have permanently discontinued study drug and have not withdrawn consent may continue in the study and complete all remaining protocol specified visits.

6.4.4 Study Drug Discontinuation Study Assessments

The site Investigator must make every effort to have the study participant return to the clinic as soon as possible after the participant permanently discontinues study drug to determine if they want to withdraw from the study. If the participant choses to withdraw from the study every attempt should be made to have all evaluations and procedures as outlined in the Schedule of Events performed. (see Table 2 in Section 4.3.1)

6.4.5 Withdrawal from Study

There are no pre-determined protocol-specific study withdrawal criteria, however, study participants may choose to withdraw from the study at any time and withdraw their consent from further participation in the study. The Site Investigator must document the reason (if specified by the participant) for the withdrawal of consent. Participants who wish to withdraw from further participation in the study should be encouraged to return to the clinic as soon as possible to complete the M12 End of Study Visit. Every attempt should be made to have all evaluations and procedures as outlined in the Schedule of Events performed. (see Table 2 in Section 4.3.1)

6.5 Concomitant Medications

Record all medications taken for treatment of study disease. Please complete a new log line each time a dose is changed.

If a screened and consented subject is started on systemic DMARD, biologic, or systemic glucocorticoids between screening and enrollment then this subject will be considered a screen failure.

6.6 Use of Oral Prednisone

A short course of oral prednisone (≤ 14 days) is allowed in the first month after enrollment or prior to enrollment if local COVID-19 conditions limit availability of intra-articular glucocorticoid injections and total active joint count is ≤ 4. Patients treated with a short course (≤ 14 days) will not be considered to have met the primary outcome for systemic medication use. Prednisone dosing should be limited to 20 mg/day.

6.7 COVID-19 Guidance

The following strategies will be employed during the clinical trial to optimize participant safety:

- Provide a fact sheet to all screened subjects on the symptoms of COVID-19
- Administer a COVID-19 questionnaire related to exposure history and physical symptoms
- Obtain and document current temperature at screening and throughout study period. If a potential subject has a temperature greater than 100.4, the subject cannot be enrolled into the trial until they have been afebrile for at least 48 hours and had negative COVID-19 testing. Subjects who develop a fever during the trial will be instructed to follow-up with their local provider for consideration of COVID-19 testing.
- The re-start of study drug after COVID-19 infection is at the discretion of the PI, following ACR guidance.
- See Section 4.9 (Immunizations) and Section 6.4.2 (Temporary Discontinuation for Study Drug) for additional information on COVID-19 guidance

- The COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force can be found at the following site: https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf

7 ASSESSMENT OF SAFETY

The sponsor has engaged DCRI Safety Surveillance to oversee real-time serious adverse event (SAE) collection, evaluation, and, as applicable, expedited regulatory reporting for this study. A medical monitor will be responsible for evaluating site reported SAEs to confirm protocol specific serious reporting criteria, causality assessment, and expectedness compared to the product label.

7.1 Definition

Only Events of Special Interest (ESIs), serious and non-serious, and SAEs will be collected for this study and reported in the RAVE EDC. COVID-19 and related symptoms that meet the criteria of an SAE will be considered unexpected/unanticipated SAEs and reported in the RAVE EDC.

Disease progression will not be reported as an ESI or SAE but will be reflected in the visit joint exams.

Safety will be assessed following initial informed consent, throughout the study and for 30 days post last study dose and it will be assessed by frequency and incidence of ESIs and SAEs. A data safety monitoring board (DSMB) will be convened to review data and safety information from study participants throughout the study.

7.2 Assessment of Adverse Event Severity

The determination of AE severity rests on medical judgment of a medically qualified investigator. The site will use the current version of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 Event severity will be assessed at event onset and event severity most extreme (CTCAE level). The severity of AEs will be graded using the following definitions:

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe but not immediately life threatening

Grade 4: Life-threatening consequences

Grade 5: Death related to AE

7.3 Assessment of Causal Relationship

A medically qualified investigator must assess the relationship of any Event to the use of study drug, based on available information, using the following guidelines:

Not related: There is not a reasonable causal relationship between the study drug and the AE.

Unlikely related: No temporal association or cause of the event has been identified, or the drug or biologic cannot be implicated.

Possibly related: There is reasonable evidence to suggest a causal relationship between the drug and AE.

Probably related: There is evidence to suggest a causal relationship between the drug and AE, and the influence of other factors is unlikely.

Definitely related: Clearly related evidence of a causal relationship between drug and AE.

7.4 Expectedness

The expectedness of an SAE shall be determined according to the most current product label. Any SAE that is not identified in nature, severity, or specificity in the current product label is considered unexpected.

7.5 Protocol-Defined ESIs

The following are commonly expected events in JIA and will not be collected as AEs, but will be reported to the study database via the SAE/ESI eCRF.

- Anaphylaxis
- Aplastic anemia
- Bleeding events requiring transfusion or hospital evaluation
- Cardiovascular event (myocardial infarction or stroke)
- Demyelinating disease
- Gastrointestinal perforation
- Hepatic Events
- Hepatitis
- Hypercholesterolemia
- Hypersensitivity reactions
- Infections treated with IV anti-infective(s)
- Inflammatory bowel disease
- Interstitial lung disease
- Leukopenia
- Lipoid pneumonia
- Macrophage activation syndrome
- Malignancy
- Mycobacterium tuberculosis infection
- Myocardial infarction
- Neutropenia
- New autoimmune disease (e.g., systemic lupus erythematosus)
- Optic neuritis
- Other opportunistic infections (Other opportunistic infections (e.g., Legionella, Listeria, systemic infections due to endemic mycoses [Coccidioides, Blastomyces, Histoplasma], Pneumocystis, Aspergillus, Nocardia, Cryptococcus, Toxoplasma, Varicella Reactivation [shingles])
- Pregnancy and pregnancy outcome
- Progressive multifocal leukoencephalopathy (JC virus)
- Psoriasis
- Pulmonary alveolar proteinosis

- Pulmonary hypertension
- Severe injection site reactions
- Stroke
- Thrombocytopenia
- Uveitis
- Worsening of autoimmune diseases (per investigator discretion)

7.6 Serious Adverse Events

A serious adverse event is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at immediate risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if more severe.

- Requires inpatient hospitalization or prolongation of 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 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 participant's general condition
- Results in disability/incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as headache, nausea, vomiting, accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect.
- Medically significant, e.g., defined as an event that jeopardizes the participant 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.

This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered an SAE).

Regardless of causality, the investigator must report within 24 hours of knowledge of the event, via RAVE EDC system, all SAEs and ESIs occurring between informed consent and Month 12 End of Study Visit or 30 days after the last dose of study drug if early termination from the study. If the eCRF system is temporarily unavailable, the SAE, including investigator-determined causality assessment, should be reported to DCRI Safety Surveillance via a paper back-up SAE form. Upon return of the availability of the EDC system, the most current SAE information must be entered into the eCRF. DCRI Safety Surveillance will notify Bristol Myers Squibb (BMS) of reported SAEs within 2 business days of awareness by DCRI Safety Surveillance.

The investigator must report, via RAVE EDC system, when important follow-up information (final diagnosis, outcome, results of specific investigations, etc.) becomes available after submission of the initial SAE/ESI information. Follow-up information should be submitted according to the same process used for reporting the initial event as described above (i.e., within 24 hours of knowledge, via RAVE EDC system). All SAEs and ESIs will be followed through resolution, stabilization, or end of study.

7.7 Reporting to Regulatory Authorities

Adverse events which meet the criteria of serious, related to study drug, and unexpected for abatacept (Orencia) per its package insert, may qualify for reporting to regulatory authorities. The site investigator will assess any SAE occurring at their site and evaluate it for relationship to study drug.

Informing US FDA: The site investigator is required to complete and submit a voluntary MedWatch Report to FDA for events confirmed by the sponsor as a suspected, unexpected, serious adverse reaction (SUSAR) at: https://www.accessdata.fda.gov/scripts/medwatch/.

Informing Health Canada: Reporting an adverse drug reaction (ADR) (i.e. a SUSAR) to Health Canada is a sponsor obligation. The sponsor or designee will notify Health Canada and all participating investigators of fatal or life-threatening SUSARs no later than 7 calendar days after receipt and of non-fatal or non-life-threatening SUSARs no later than 15 calendar days after receipt via a CIOMS I Form.

Informing the IRB/REB: The site investigator will be responsible for reporting serious adverse events and unanticipated problems involving risks to study participants to their local IRBs/REBs in accordance with local regulations.

7.8 Pregnancy

If, following initiation of abatacept (Orencia), it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of abatacept (Orencia) exposure, or within 5 half-lives (66 days) after product administration, abatacept (Orencia) will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

During the course of the trial, female study participants will be instructed to contact the site investigator immediately if they become pregnant. The study participant will discontinue study drug. The site investigator must report any pregnancy occurring during the trial on the appropriate Pregnancy Surveillance Form. While pregnancy is not considered an SAE, it must be reported within 24 hours of knowledge of the pregnancy, the same timelines as an SAE. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and infant. The Site PI is responsible for following the participant's pregnancy to final outcome. DCRI Safety Surveillance will notify BMS of any pregnancy within 2 business days of awareness by DCRI Safety Surveillance. Any associated SAEs/ESIs that occur to the mother or fetus/infant will be recorded on the SAE/ESI eCRF, as appropriate.

8 EFFICACY ASSESSMENTS

8.1 Primary Outcome

The primary outcome is the occurrence of any of the following: polyarthritis, active anterior uveitis, or initiation of systemic DMARDs and/or biologics, including systemic glucocorticoids (IV or PO) within 12 months of enrollment.

(a) Polyarthritis is defined as a cumulative total of ≥5 active joints with arthritis since disease onset. The active joint count will be assessed at each study visit from baseline through month 12. Active arthritis is defined as joints with swelling not due to bony enlargement or joints with limitation of motion accompanied by either pain on motion and/or tenderness. For the purposes of counting affected joints, each toe counts as a single joint irrespective of whether it is the proximal interphalangeal joint (PIP), the distal interphalangeal joint (DIP), or both that are affected, consistent with previous clinical trials. Joint counts will be documented using a dedicated case report form (eCRF) at each study visit, tracking both specific joints and number of joints involved.[61]

(b) The presence of active anterior uveitis, defined according to the Standardization of Uveitis Nomenclature for Reporting Clinical Data (SUN criteria) as the presence of one or more cells in each 1mm x 1mm slit beam field (Grade 0.5+, trace cells), [62] will be assessed at standard of care ophthalmology visits as described by the Heiligenhaus modification of the American Academy of Pediatrics recommendations (see Table 2 in Section 4.3.1). Results will be collected using the existing CARRA Registry uveitis specific eCRF.

(c) Use of systemic DMARDs and/or biologics, including systemic glucocorticoids (IV or PO) will be captured on the concomitant medication eCRF at each study visit.

8.2 Secondary Outcomes

8.2.1 Patient reported outcomes

Patient-reported outcomes (PROs), related to pain, fatigue, functional ability, anxiety, depression, global health, family impact, and other medication side effects will be collected and analyzed. PROMIS® measures will be used for each of the outcomes of interest where available. Caregiver/proxy-report will be obtained for participants able to complete the forms in English or in Spanish, and by self-report for children ≥ 8 years of age. The existing iPAD-based, CARRA Registry electronic PRO system will be utilized.

The following PRO instruments will be used.

- PROMIS® pediatric measures selected by the patient/family partners (pain interference, fatigue, functional ability) that have undergone preliminary validation in JIA.[64,65]
- PROMIS® pediatric measures of anxiety, depression, and global health.
- Side effects of medications, assessed by the yes/no question 11 in the JAMAR.[66]

Table 5: Description of PROs

Outcome	Measure	Timing	Source
Pain	PROMIS® pediatric pain interference	Every study visit	Parent-proxy or child (if ≥ 8 years)
Fatigue	PROMIS® pediatric fatigue; short form	Every study visit	Parent-proxy or child (if ≥ 8 years)
Functional Ability	PROMIS® upper extremity function and mobility	Every study visit	Parent-proxy or child (if ≥ 8 years)
	CHAQ	Baseline, 6M, 12M	Parent-proxy or child (if ≥ 8 years)
Anxiety	PROMIS® pediatric emotional distress – anxiety; short form	Baseline, 6M, 12M	Parent-proxy or child (if ≥ 8 years)
Depression	PROMIS® pediatric emotional distress – depression; short form	Baseline, 6M, 12M	Parent-proxy or child (if ≥ 8 years)
Global Health	PROMIS® pediatric global health measure (PGH-7)	Every study visit	Parent-proxy or child (if ≥ 8 years)
Other medication side effects	JAMAR (Juvenile Arthritis Multidimensional Arthritis Report) question #11	Baseline, 3M, 6M	Parent-proxy or child (if ≥ 8 years)

8.2.2 Enhanced Study Recruitment (US Based Sites Only)

The outcome for screening efficacy using enhanced study recruitment will be assessed as the marginal difference for successful identification of study participants who meet the limited JIA inclusion criteria. We will compare absolute and relative numbers of eligible participants identified by computable phenotype augmented screening lists vs screening lists generated by current, ad-hoc processes alone. In addition, the efficiency of augmented screening will be assessed as the number of additional records requiring manual screening and chart review in order to identify one additional eligible participant.

8.2.3 Data Completeness

The main outcome for data completeness will be the rate of missing data utilizing same-site comparison. We will assess and compare the relative differences in data completeness by data elements of interest (i.e. hospitalizations, abnormal lab values of interest, occurrence of infections) before and after EHR data linkage at participating sites. Additional outcomes may include metrics of research coordinator time required to achieve various thresholds of data

completeness across sites that utilize data linkage in comparison to sites that do not employ data linkage. For sites not employing data linkage, study data of representative samples of enrolled study participants may be analyzed via chart review of EHR data to estimate the completeness of data.

8.2.4 Other Secondary Outcomes

Other outcomes describing the clinical course of study participants will include

- Proportion of children achieving clinical inactive disease and/or remission
- Number of new joints with arthritis.
- Cumulative number of glucocorticoid joint injections.
- Serious adverse events.
- Juvenile arthritis disease activity (JADAS) scores.
- Elapsed time from enrollment to disease extension, uveitis or systemic medication use.
- Proportion of participants with disease extension (development of polyarthritis or uveitis).

9 STATISTICAL ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

9.1 Statistical Design

The primary objective of LIMIT-JIA is to evaluate the effectiveness of a 24-dose course of abatacept (Orencia) plus usual care (including NSAIDs and/or intra-articular glucocorticoids) versus usual care alone, to prevent development of polyarthritis or uveitis, or initiation of treatment with other systemic medication(s) for JIA (i.e. one or more of the following: systemic glucocorticoids, DMARD or biologic) within 12 months of enrollment in children with recent-onset limited JIA.

Secondary objectives include comparison of participants and caregiver reported outcomes between the different treatment strategies.

The analysis population will include data from two parts of Limit-JIA. In Part I participants were randomly assigned to receive abatacept + usual care or usual care alone. Part II participants will all be assigned to receive abatacept + usual care.

Part I enrolled participants into a randomized open-label multicenter trial with a planned sample size of 306 JIA participants recruited from CARRA Registry sites. Participants were randomly allocated (1:1) to receive 24 weeks of abatacept plus usual care or usual care alone. Randomization was stratified on uveitis risk (higher and lower) and polyarthritis risk (higher and lower). Upon completion of 24 weeks of randomized treatment, each participant was to receive usual care and undergo follow-up for assessment of outcomes for an additional 12 months. Planned duration of the study for each participant was 18 months. Due to slow accrual and apparent loss of equipoise, enrollment into Part I has been discontinued 17February2022 As of October 29, 2021, 37 participants have been randomized in Part I. Part I participants will continue follow-up as planned.

Part II is a non-randomized continuation of LIMIT-JIA with planned enrollment of 80 evaluable participants receiving abatacept. Participants will receive 24 doses of abatacept plus usual care. Upon completion of 24 doses, each participant will receive usual care and undergo follow-up for assessment of outcomes for an additional 6 months. Planned duration of the study for each participant is 12 months. Part II will assess the efficacy of abatacept in prevention of disease extension by comparison of outcomes between participants enrolled in the abatacept arm and 428 CARRA Registry patients who would have met major eligibility criteria for LIMIT-JIA.

Statistical analysis of this study is planned upon study completion, when all participants in Part II have completed 12 months of follow-up or have withdrawn from the study.

Definition of analysis population will follow intention-to-treat (ITT) principles including, as much as possible, all enrolled participants evaluated for the outcome(s) being analyzed. An exception will be for safety analyses, wherein participants will be included corresponding to treatment actually received.

9.2 Primary Analysis

The primary outcome is the proportion of participants experiencing disease extension, (development of polyarthritis or uveitis, or initiation of systemic medications during the 12-month period following enrollment). Participants will undergo evaluations for polyarthritis every 3 months during the 12-month duration of the study. Ophthalmological examinations for uveitis will be performed for enrolled participants according to the schedule in Table 3.

The primary analysis will compare the disease extension rate in the group of patients assigned to receive abatacept in Part II to a weighted average of disease extension rates observed in 6 cohorts (total of 428 patients) from the CARRA Registry who would have met the entry criteria for LIMIT-JIA. [See Appendix: Modification of Study Design and Rationale for Discontinuing Randomization to Control Arm]

The primary analysis will use the logistic regression model, $\log(\pi / (1 - \pi)) = TRT$, where TRT is the assigned treatment arm (abatacept or control). This analysis will test the null hypothesis that the disease extension rates in the abatacept and control arms are equal. The odds ratio with 95% confidence limits will describe the estimated treatment effect.

A secondary analysis of the disease extension rate will include a stratification factor for Part (I or II) and an interaction term (TRT x PART). This analysis will assess the homogeneity of treatment effect between Part I and Part II. Due to the small number of participants randomized to the control arm, statistical power to detect a TRT x PART interaction is limited.

For Parts I and II, the analysis population for the primary endpoint will consist of participants whose disease status is determined at 12 months. In case some participants are not evaluated at 12 months, sensitivity analyses may be performed including simulated data for the participants with unobserved primary outcome. Simulations will be conducted under a variety of assumptions about the distribution of the unobserved outcomes including 1) under the null hypothesis, 2) under alternative hypotheses unfavorable to the abatacept plus usual care treatment arm and, if appropriate, 3) according to plausible patterns determined by taking into account factors such as baseline disease status, length of follow-up, and magnitude and variance of estimated treatment effect from observed data. Non-random patterns of missing data may be considered. If the estimated treatment effects and conclusions from hypothesis testing are generally consistent between the primary and sensitivity analyses, the primary analysis will be considered accurate.

Methods used to account for missing data will be described in more detail in the Statistical Analysis Plan.

9.3 Major Secondary Analyses

Secondary analyses will be done for two study populations. Participants randomized in Part I or assigned to the abatacept arm in Part II will comprise the enrolled population [N approximately equal to 126 (37 Part I, 89 Part II]. The overall study population [N approximately equal to 554] will include the enrolled population and 428 patients from the CARRA Registry whose disease extension results provided the control mean in Part II.

Secondary analyses for the enrolled population

Secondary analyses will generally be conducted as planned in Part I, although estimation of treatment effects or treatment by factor differences will be imprecise, since more than 80% of participants in the enrolled population are expected to receive abatacept.

Description of the time to disease extension will include cumulative incidence curves for the composite primary outcome and for the components disease extension, uveitis, and initiation of DMARDs or other biologic medication.

Descriptive analyses will summarize participant and caregiver reported outcomes (continuous outcomes of pain interference, fatigue, upper extremity function, mobility, anxiety, depression and global health PROMIS® modules, medication side effects (JAMAR), and the CHAQ). These outcomes will be measured at baseline and follow-up visits as shown in Table 5, and will be analyzed using a mixed model for repeated measures. Preliminary analyses will be performed to identify a parsimonious covariance structure among the repeated measures. The model will include as fixed effects treatment, time, treatment x time interaction, the baseline value of the outcome and the two stratification variables, the risk categories for polyarthritis and uveitis. Time will be treated as a categorical variable. The restricted maximum likelihood (REML) method of estimation and the Kenward-Roger degrees of freedom correction will be used. Contrasts will be constructed among the model parameters to test specific hypotheses. Overall treatment effect will be assessed by testing the null hypothesis of no treatment difference averaged over time. If the treatment x time interaction is significant at α=0.10, additional descriptive tests may be done for treatment differences at specific time-points. Since more than 80% of participants in the enrolled population are expected to receive abatacept, there will be limited statistical power to determine treatment effects on these outcomes.

Secondary analyses for the overall study population

Inclusion of data from 428 CARRA Registry patients may provide important information on the impact of treatment on time to disease extension and PROs. Since treatment assignment for the overall study population is not random, it is anticipated that causal inference techniques such as inverse probability or overlap weighting will be useful in determining the comparability of the Registry patients and participants enrolled in LIMIT-JIA.

The timing of evaluations for disease extension and PROs and missing data patterns are expected to differ between participants enrolled in LIMIT-JIA and CARRA Registry patients. Techniques such as multiple imputation may be used to enable modeling of the overall study population.

Details of the analysis of treatment effect for the overall study population will be provided in a separate SAP.

9.4 Other Planned Analyses

Other planned analyses for the enrolled population

In addition to assessment of treatment differences in PROs, other secondary outcomes include proportion of children achieving clinically inactive disease and/or remission; number of new joints with arthritis; cumulative number of glucocorticoid joint injections; serious adverse events; juvenile arthritis disease activity (JADAS) scores; elapsed time from enrollment to disease extension, uveitis or initiation of DMARD or other biologic treatment.

Sensitivity analyses will be performed to assess the impact of COVID-19 – including measures taken in response to the pandemic such as telehealth visits, missed visits or oral prednisone use on the primary study endpoint. COVID-19 infections will be included in the safety analyses.

Other planned analyses for the overall population

To be described in a separate SAP.

9.4.1 Subgroup Analyses

Subgroup analyses for enrolled population

For the primary composite outcome, a formal test of homogeneity of treatment effect among baseline risk categories is planned. Exploratory comparisons will be carried out in the ITT population for the primary outcome, the components of the primary outcome, and for the two primary PROMIS® measures (pain interference and mobility), comparing the results between subgroups in order to determine clinical and biological factors associated with each. Subgroups will include the different ILAR categories of JIA (enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis compared to oligoarthritis); demographic factors (age, sex, race); inflammatory markers at time of enrollment (normal or elevated ESR, CRP); presence or absence of autoantibodies (antinuclear antibody, rheumatoid factor, ccp); genetic marker human leukocyte antigen B27 (HLA-B27); the number of joints and specific joints affected prior to enrollment; and the duration of disease prior to enrollment. Statistical comparison of treatment effects in subgroups will be done by the addition of a term denoting subgroup membership in the model used to compare the two treatment arms. We will test the subgroup-by-treatment interaction at the 0.15 level. Graphical displays such as forest plots, showing treatment effects and 95% confidence limits within subgroups may be used to display results. The subgroup analyses in this study are exploratory and should be considered hypothesis-generating.

Subgroup analyses for the overall study population

To be described in a separate SAP.

9.4.2 Power, Sample Size and Type I error

The trial sample size was determined by the intended statistical comparison of the primary outcome (proportion of participants with disease extension) between the abatacept plus usual care and historical care usual care treatment arms [See Appendix: Modification of Study Design and Rationale for Discontinuing Randomization to Control Arm]. It is assumed that the proportion of participants with disease extension will be 34.3% in the usual care arm, and that

this rate will be reduced to 15% in the abatacept plus usual care arm. With 1-sided type 1 error = 0.025, 80 evaluable participants enrolled into the abatacept + usual care arm (compared with the historical control mean from 428 patients) would provide > 95% power using logistic regression. Assuming 10% of participants will not be evaluable, we will enroll up to 89 patients to receive abatacept + usual care arm. See Table 7. Hypothesis testing will be done with the Wald statistic testing the effect of the factor for treatment (abatacept + usual care, vs usual care) in the logistic model with factors for intercept and treatment.

Subgroup or other non-primary analyses may be done by inclusion of additional factors to the logistic regression model.

Table 7: Simulated power for sample sizes in the experimental arm of 10, 20, …, 80; assuming type I error = 0.025 one-sided.

Sample size (evaluable) in experimental arm N =	Number to enroll assuming a 10% inevaluable rate	Power *
20	23	0.332
30	34	0.591
40	45	0.742
50	56	0.824
60	67	0.900
70	78	0.934
80	**89**	**0.956**

* For R_{ex} and R_c = disease extension rates in the experimental and control arms, resp. H_0: $R_{ex} = R_c = 0.343$ (estimated from the historical control group), and H_1: $R_{ex} < 0.15$ (i.e. $< R_c - 0.193$). Power was calculated by simulation of the logistic model, where extension rates followed a binomial distribution [$R_c = 0.343$, N = 428] in the control arm, and [$R_{ex} = 0.15$, N (for N = 20, 30, …,80 as shown in the table)]. Type I error is 0.025, one-sided.

A sample size of eighty evaluable patients (all enrolled in the abatacept + usual care arm) will provide > 95% power to reject the null hypothesis that the disease extension rate is ≥ 34.3 % assuming one-sided type I error ≤ 0.025 and a true disease extension rate in the abtacept + usual care arm ≤ 15%. To allow for an inevaluable rate up to 10%, enrollment will be expected to be approximately eighty-nine patients.

9.5.4 Interim Analysis

Interim analyses, with stopping boundaries for futility and efficacy, are planned after approximately 40% (n = 32) and 80% (n = 64) of Part II participants have been followed for one year. Details will be provided prior to initiation of Part II.

10 DATA AND SAFETY MONITORING

10.1 Data Safety Monitoring Board

An independent DSMB will monitor the progress of the study and ensure that it meets the highest standards of ethics and study participant safety.

The DSMB will be formed specifically to oversee trial progression with regards to serious adverse events and events of special interests. Responsibilities of the DSMB will include review of accumulated safety data and assessments to ensure the safety of study participants and overall integrity of the study, provide recommendations regarding the further conduct of the study and identify safety issues which may suggest risk to the participants already enrolled in the study or prospective participants. A DSMB charter will outline the membership, responsibilities, scope of activities, meeting frequency and communication plan between committee, sponsor and study sites. There will be three members of the DSMB who will collectively have competence and experience of JIA disease (in children), conduct of clinical studies, and interpretation of clinical study data

Membership, functions and operating procedures of DSMB and other organizational groups for this study will be defined in a separate document. Operating procedures for the DSMB will be established before the first review of the data.

10.2 Required Data

All required data for the clinical objectives of the study will be entered into the electronic case report form (eCRF). All required data for the PRO surveys will be collected per the CARRA Registry protocol. All required data for the patient entered data will be entered via the MyStudies app through their personal device or via a paper diary supplied by the study and then manually entered by the study team.

10.3 Data Collection and Tracking

Data will be collected directly from participants (via paper or electronic questionnaires and/or personal interview) during study visits as well as via electronic entry on their mobile devices using the MyStudies App or paper diaries between study visits. Data collection may be supplemented by data extracted from the study participant’s medical record from dates on, before, between, and subsequent to baseline and follow up visits.

11 STUDY RESPONSIBILITIES

11.1 Investigator Responsibility/Performance

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

1. Grant sponsor or their delegate access to study participant records to verify the entries on the eCRF
2. Ensure the accuracy, completeness, and timeliness of data reported to the sponsor in the eCRFs, including reporting of SAEs and ESIs
3. Assure appropriate safeguarding of participants health information
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 study participant 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.

Investigators agree to have and use 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 study.

11.2 Study Documentation

Participant source documents are the physician's study participant records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's medical records. The information collected on the CRFs must match those source documents. In some cases, a portion of the source documents for a given study participant may be the CRF or participant diary (electronic app or paper diary).

11.3 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. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of site personnel to use continuous vigilance to identify and report deviations to the sponsor.

All deviations from the protocol must be addressed in study case report forms. A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB/IEC per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

11.4 Study Drug Accountability

In accordance with local regulatory requirements, the pharmacy, Site Investigator or designated site staff must maintain accurate records demonstrating receipt of study drug, date and amount of study drug received, to whom and by whom administered or dispensed (participant accounting) and accounts of returned study drug and any study drug accidentally or deliberately destroyed. Study drug accountability records must be maintained throughout the course of the study.

At the end of the study period, neither the sponsor nor Bristol-Myers Squibb Company will continue to supply study drug to participants/Site Investigators unless the study is extended. The site investigator is responsible to ensure that the participant receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Site Investigator to treat the condition under study.

11.5 Study Closeout

The end of the study is when the last study participant completes the last visit.

Upon completion of the study (defined as all study participants have completed all follow-up- visits, all eCRFs are complete, and all queries have been resolved), the sponsor will notify the site of closeout, and a study closeout visit will be performed. At the end of the study, any remaining study drug will be destroyed locally. A certificate of destruction must be issued and provided to the sponsor. The sponsor's monitor will ensure that the Site PI's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

11.6 Publication Policies

The sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations.

11.7 Record Retention

The investigator should maintain a record of the location(s) of essential documents as defined in the ICH GCP Guideline including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before during and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system using during the study and for archiving (irrespective of the type of media used) should provide for document identification version history, search and retrieval. The data will be available for evaluation and/or audits from Health authorities, the sponsor or sponsor representatives.

The records should be retained by the investigator according to local regulations or as specified in the Clinical Trial Agreement.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to the sponsor.

12 ETHICAL CONSIDERATIONS

12.1 Informed Consent

Before any study-related activities are initiated, consent will be obtained from all participants who can provide legally effective consent. For participants who are under the age of majority, parental permission will be obtained from a parent or legal guardian on the participant's behalf and the child's assent will be obtained per local requirements. If a study participant attains the age at which she/he can provide legally effective consent under applicable state law, the participant will be asked to provide informed consent on his/her own behalf.

12.2 Confidentiality of Study Participants

Study participant confidentiality will be maintained throughout the study. A unique participant identification code will be used that allows linkage of all data reported for each participant.

To protect study participant confidentiality, research datasets will be maintained as coded or de-identified data, and linkages between research datasets and medical record numbers will be limited to appropriately trained staff using approved mechanisms for medical record review. Linkage tables between coded identifiers and medical record numbers will be maintained separately from the research datasets. Medical chart reviews will take place at the site level only and only designated, trained individuals approved by the local IRB/REB will be allowed to access these charts for purposes of review and validation. Abstracted data from medical record review will be recorded with the coded study participant identifiers only. All data will be housed in approved locations and electronic systems.

Participant information collected in this study will comply with all national and local laws and regulations. . All records will be kept confidential and secure. Participant records will not be released to anyone other than the sponsor, authorized CARRA Registry and Limit-JIA research study personnel, and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure participants' data are treated confidentially and in keeping with established, industry-standard data privacy practices.

12.3 Institutional Review Board/Ethics Committee Review

Before initiating this study, the protocol, site-specific informed consent/assent forms, HIPAA Authorization forms (US only), recruitment materials, and other relevant information will be reviewed by a properly constituted IRB/REB or reliant IRB for each participating clinical site. Documentation of IRB approval for this protocol, site-specific informed consent/assent forms, HIPAA Authorization forms, recruitment materials, study participant questionnaires and any other material reviewed by the site's IRB/REB will be sent to and reviewed by the sponsor before site initiation. Any amendments to the protocol, and/or revisions to the informed consent documents will be approved by each IRB/REB before local implementation. The site investigator will provide the sponsor with documentation of all IRB approvals.

12.4 Information Security

All sites will follow their institution's guidelines for data security and confidentiality. Other than CARRA Registry participant contact information and identifiers used for purposes of participant data linkage, which are captured in the web-based research subject management platform used for all CARRA Registry subjects according the policies and procedures regulated by the CARRA Registry protocol at participating sites, all direct identifiers will remain at the local site. Each site in the network has infrastructure in place to monitor and ensure data security, including HIPAA requirements (US only).

The participating sites involved in computable phenotype and/or EHR data completion aims will use their clinical data warehouses and/or EHR systems to generate disease-specific cohort lists. A set of study participant coded identifiers will be generated; appropriately authorized site staff will then use these coded subject identifiers to generate an EHR data set consisting of the requested EHR records for study participants. For the medical chart review validation process, the authorized site staff will generate a cross-reference table linking the coded identifiers to the study participants' medical record numbers, which will be made separately accessible to the site PI and/or his/her approved designates at each site. While data available for review may vary across sites, the anticipated categories of information to be reviewed include: diagnoses, procedures, pathology results, encounters, labs, vitals, medications, clinical notes, x-rays, and demographics.

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