PEDIATRIC UVEITIS STUDY

A Study of Uveitis in Children <18 Years of Age

Protocol Identifying Number: UV1

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KEY ROLES

Protocol Co-Chair	
Name, degree	Kara C. LaMattina, M.D.
Title	Director of Uveitis and Pediatrics Services
Institution Name	Department of Ophthalmology, Boston University School of Medicine Boston Medical Center 85 E. Concord Street, 8th floor Boston, MA 02118 Email: Kara.lamattina@gmail.com
Protocol Co-Chair	
Name, degree	Virginia Utz, M.D.
Title	Professor of Pediatric Ophthalmology
Institution Name	Cincinnati Children's Hospital Medical Center Abrahamson Pediatric Eye Institute 3333 Burnet Avenue | MLC 4008 | Cincinnati, OH 45229 Email: Virginia.utz@cchmc.org
JCHR Principal Investigator	
Name, degree	Julianne Zawadzki, M.S.P.H.
Title	Epidemiologist
Institution Name	Jaeb Center for Health Research 15310 Amberly Drive, Suite 350 Tampa, FL 33647 Phone: 1-888-797-3344 Email: jrobinson@jaeb.org http://www.pedig.net

VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	J. Zawadzki	R.Kraker	16Dec2025	Initial version.
1.1	J. Zawadzki	R. Kraker	1Jan2026	Updated to reflect proxy questionnaire now administered to all parents regardless of child's age.
1.2	J. Zawadzki	R. Kraker	30Jan2026	Updated protocol to provide clarification on study definition of uveitis and steroid control. Added section 2.4.1 to note questionnaire administration procedures. Typographical errors corrected throughout.

*Version in effect at study initiation

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Anterior chamber
AUS	American Uveitis Society
BCVA	Best corrected visual acuity
CFR	Code of Federal Regulations
CGRN	Childhood Glaucoma Research Network
CME	Cystoid macular edema
CMV	Cytomegalovirus
CRF	Case report form
DMARDs	Disease-modifying antirheumatic drugs
eCRF	Electronic case report form
FA	Fluorescein angiogram
FIPS	Federal information processing system
GCP	Good clinical practice
HSV	Herpes simplex virus
ICH	Intracranial hypertension
IOP	Intraocular pressure
IRB	Institutional Review Board
JIA	Juvenile idiopathic arthritis
JXG	Juvenile xanthogranuloma
LP	Light perception
mmHg	Millimeters of mercury
MTX	Methotrexate
MUST	The Multicenter Uveitis Steroid Treatment
NIU	Non-infectious uveitis
OCT	Optical coherence tomography
QA	Quality assurance
QC	Quality control
SUN	Standardization of Uveitis Nomenclature
TNF	Tumor necrosis factor
UBM	Ultrasound biomicroscopy
VA	Visual acuity
VZV	Herpes zoster

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	A Study of Uveitis in Children <18 Years of Age (UV1)
Précis	The rarity of pediatric uveitis creates a pressing need for a multicenter cross-sectional observational study to collect data in children regarding the prevalence of uveitis subtypes, current treatment approaches, and patient-reported outcome measures. Such information will be instrumental for the planning of future randomized clinical trials.
Objective	Over a one-year period, to enroll children diagnosed with uveitis and collect data regarding clinical features and current and past treatments at time of enrollment. A medical record review will be conducted 12 months after enrollment for any children with new onset non-infectious uveitis (onset within 6 months prior to enrollment).
Study Design	Multicenter observational study.
Number of Sites	The study is open to Pediatric Eye Disease Investigator Group (PEDIG) sites and sites affiliated with the American Uveitis Society (AUS).
Specific Aims	The specific aims of this observational study are to: 1. Describe the frequency of uveitis subtypes in children <18 years of age, including new onset uveitis (<6 months duration). 2. Describe clinical and demographic characteristics overall and within each type of uveitis. 3. Compare characteristics between uveitis subtypes. 4. Describe current and previous treatment history by type of uveitis. 5. Describe clinical measures done as part of usual care. 6. Determine recruitment potential overall and by site for different disease sub-types (new-onset vs. established disease, localization, etiology) for future randomized clinical trials. 7. Evaluate relationships between demographic, treatment, and clinical characteristics and quality of life as measured by the EYE-Q (current version) questionnaire. 8. Develop a comprehensive PEDIG Uveitis Quality of Life questionnaire by administration and calibration of EYE-Q plus additional uveitis-specific and treatment related items.

PARTICIPANT AREA	DESCRIPTION

Population	**Key Inclusion Criteria:**
	• Age:
	  ○ Incident cases (onset ≤ 6 months) <17 years
	  ○ Established cases (onset > 6 months) <18 years
	• Diagnosis of any type of uveitis in any location except traumatic and post-operative uveitis
	• Active or inactive uveitis with any treatment status (current / prior / none [but under surveillance])
	
	Key Exclusion Criteria:
	• Bilateral uveitis with differing etiologies
	• Traumatic uveitis
	• Post-operative uveitis
	• Coexisting ocular and systemic conditions allowed except retinoblastoma, Coat's disease, retinitis pigmentosa, inherited retinal degeneration, juvenile xanthogranuloma (JXG), or leukemia/malignancy within the eye

Sample Size	The study will recruit up to 300 participants with uveitis over a one-year enrollment period.
Phase	Observational study.
Treatment Groups	Not applicable. Enrollment of children diagnosed with uveitis, either active or inactive with or without current treatment at time of enrollment.
Participant Duration	Single enrollment only followed by a chart review 12 months after enrollment for children with new onset non-infectious uveitis (onset within 6 months of enrollment).
Protocol Overview/Synopsis	The protocol establishes an observational study to collect data on children and teenagers who have been diagnosed with uveitis in at least one eye. Informed consent, screening for eligibility, and enrollment into the study occurs after uveitis diagnosis in at least one eye has been confirmed as part of usual care. Current and past history data will be collected from medical record review at the time of enrollment followed by a medical record review 12 months after enrollment for children with new onset non-infectious uveitis (onset within 6 months prior to enrollment). Clinical assessment will mimic usual care.

2 STUDY SUMMARY FLOW CHART

MAJOR ELIGIBILITY CRITERIA

- Age:
  - Incident cases (onset ≤ 6 months) <17 years
  - Established cases (onset > 6 months) <18 years
- Diagnosis of any type of uveitis in any location (except traumatic and post-operative uveitis)
- Active or inactive uveitis with any treatment status (current / prior / none [but under surveillance])
- Coexisting ocular / systemic conditions allowed except retinoblastoma, Coat's disease, retinitis pigmentosa, inherited retinal degeneration, juvenile xanthogranuloma (JXG), or leukemia/malignancy within the eye

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ENROLLMENT

- Medical & treatment history (including prior surgical procedures)
- Classification of uveitis type
- Current treatment (systemic and ocular)
- Weight
- Clinical measures:
  - Best corrected visual acuity
  - Intraocular pressure
  - Pupil exam
  - Slit lamp exam by investigator's usual method
    - Primary location(s) of uveitis as determined by SUN[1]
    - Grading of cell count and flare per SUN criteria pre-dilation.[1]
    - Grading of vitreous cell post-dilation
  - Dilated fundus exam with indirect ophthalmoscopy
    - Vitreous haze
    - Retinal exam
- Additional clinical measures (if done as usual care)
  - Strabismus Exam
  - Refraction
- Ancillary testing (Y/N) (if done as usual care)
- Ocular complications present (Y/N)
- Quality of life questions (EYE-Q with additional items from literature review)
  - Child Questionnaire completed by children 8 to <18
  - Parent Proxy Questionnaire completed by parent for all children
  - Parent Questionnaire completed by parent for all children

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MEDICAL RECORD REVIEW – 12 MONTHS POST-ENROLLMENT

- Only for children with new onset non-infectious uveitis onset within 6 months prior to enrollment.
- Follow-up visits after enrollment will be performed according to the clinical center's usual routine.
- No procedures will be performed specifically for the study except that for children with new onset non-infectious uveitis (onset within 6 months prior to enrollment), participating sites will be asked to perform a medical record review 12 months after enrollment to collect clinical data that is part of usual care.
- Data collected will include medical, medication, and eye treatment history; and ocular examination data including best corrected visual acuity in each eye.

STUDY PROCEDURES

	Enrollment	12-Month Chart Review*
Informed Consent / Assent (if needed)	X	
Demographics	X	
Medical and Treatment History (including prior surgical procedures)	X	X
Classification of Uveitis (type, location, severity, control)	X	X
Weight	X	X
Clinical Measures:		
Best Corrected Distance Visual Acuity (investigator's usual method)	X	X
Intraocular Pressure	X	X
Pupil Exam	X	X
Slit Lamp Exam (Grading of cell count and flare per SUN criteria[1])	X	X
Dilated fundus exam (Grading of vitreous cell by Slit Lamp Exam, vitreous haze by indirect ophthalmoscopy)	X	X
Additional Clinical Measures *(by investigator's usual method, if done as usual care)* - Strabismus Assessment - Refraction	X	X
Ancillary imaging (If done as usual care, Yes or No only): - OCT retina/macula - OCT optic nerve - Color photos - Fluorescein angiogram (oral or IV) - Visual field - Brain MRI - Ultrasound UBM or B-scan - Indocyanine Green angiography - Autofluorescence - A-scan (axial length for glaucoma) - Electroretinogram	X	X
Ocular Complications for Each Eye (Yes or No): - Band keratopathy - Synechiae - Cataract - Ocular hypertension - Glaucoma/Glaucoma Suspect - Ocular hypotony - Optic disc edema - Macular edema - Epiretinal membrane formation - Vasculitis/vascular leakage - Other	X	X
Current Treatment (systemic and ocular)	X	X
EYE-Q questionnaire with additional quality of life questions		
- Child Questionnaire completed by children 8 to <18	X	
- Parent Proxy Questionnaire completed by parent for all children	X	
- Parent Questionnaire completed by parent for all children	X	

*For children with new onset non-infectious uveitis (onset within 6 months of enrollment): Data will be collected 12-months following enrollment from data collected at standard care visits since enrollment When applicable, if more than one element is available for a report field, the most recent element will be reported.

Chapter 1: Background Information

1.1 Epidemiology

Uveitis is an ocular inflammatory disease affecting the uvea, which is anatomically composed of the iris, ciliary body, and choroid. Uveitis in children is rare with reported annual incidence estimates in those <16 years of 4.3/100,000 in a UK population,[2] 14/100,000 person-years (95% CI, 11.3–16.5) in a Finnish population,[3] and 6.9/100,000 person-years in Northern California.[4] Annual incidence is reported to increase with age, with estimates of 3.15, 3.84, and 6.06 per 100,000 in patients from < 5, 6 to 10, and 11 to 15 years old, respectively.[2]

1.2 Classification

Uveitis is classified as non-infectious or infectious depending on etiology. In the US, the majority of pediatric uveitis cases are noninfectious. A retrospective analysis based on insurance claims estimated the prevalence of non-infectious uveitis [NIU] in children to be 29/100,000 (95% CI, 26.1-33.2).[5] The pathogenesis of NIU is presumed to be autoimmune or autoinflammatory. The most common systemic disease associated with pediatric NIU is juvenile idiopathic arthritis (JIA), present in 50-80% of uveitis cases.[6-8] Pediatric NIU in the US is commonly bilateral (75%), anterior, chronic, and is often challenging to diagnose and treat.[9]

Infectious uveitis is much less common in the US, accounting for 3.4-24.3% of pediatric cases.[8-10] Causes of infectious uveitis include toxoplasmosis, toxocariasis, Lyme disease, herpes simplex virus (HSV), cytomegalovirus (CMV), herpes zoster (VZV), syphilis, *Bartonella*, rubella, and tuberculosis.[6,9]

Cases with no known associated systemic disease are referred to as undifferentiated (previously termed idiopathic) uveitis. In the US, up to 27-51% of children with uveitis have undifferentiated uveitis,[9] signifying no identifiable associated systemic or ocular disease.

1.3 Clinical Characteristics

Uveitis is characterized by inflammation of the iris, ciliary body, and/or choroid and is classified anatomically, histopathologically, and by descriptors of onset, duration, and clinical course using the definitions developed by the Standardization of Uveitis Nomenclature Working Group.[1]

Anterior uveitis is characterized by white blood cells generally with concomitant protein (flare) in the anterior chamber. Intermediate uveitis is characterized by inflammation primarily located in the vitreous cavity. Intermediate uveitis is further subclassified into pars planitis and non-pars planitis type.[1,11,12]

Posterior uveitis is characterized by primary retinal or choroidal inflammation. Panuveitis is defined as inflammation of the anterior, intermediate, and posterior segments of the eye.[1]

1.4 Signs and Symptoms

The clinical presentation varies depending on the anatomic location and phenotype. For example, the onset of JIA-associated chronic anterior uveitis is often insidious with few symptoms.[13] However, children with other forms of uveitis may have eye redness, decreased vision, floaters, pain, and photophobia.[9,14] Visual acuity (VA) may be significantly impaired even at presentation:

one US-based study[15] (n=469 eyes; tertiary referral center) reported 20% of eyes were 20/50 to 20/200 and 8% had 20/300 to light perception (LP) vision at presentation with no LP in 1%. A study of 527 eyes[8] reported 9.23% were 20/200 or worse at presentation, and in a review of 196 eyes with JIA-associated uveitis,[16] 18% of eyes were "legally blind" (20/200 or worse) at presentation.

Complications may be present at the time of NIU diagnosis, including cataracts, band keratopathy, synechiae, hypotony, glaucoma, and cystoid macular edema (CME).[17-19] Stroh *et al*.[16] found 79 of 196 eyes (40.3%) with JIA-associated uveitis had ocular hypertension or secondary glaucoma at presentation to a tertiary care center.

1.5 Current Practice

The primary goal of treatment for NIU is to control inflammation and prevent ocular complications. A stepwise treatment approach is adopted to reduce the risk of potential local and systemic side effects. Typically, topical or oral glucocorticoids are initiated as first-line treatment, with the addition of other therapies as dictated by clinical disease and course. Prolonged use of topical steroids can lead to the development of cataracts and glaucoma,[16,20] with systemic steroids attributing additional risks of weight gain, mood disorders, and growth retardation. Inadequate response to glucocorticoids, the development of new or worsening complications, and failure to successfully taper steroids without recurrence of uveitis are all indications to escalate to disease-modifying antirheumatic drugs (DMARDs) to improve vision outcomes. If non-biologic DMARD treatment fails, biologic DMARD therapy (typically with tumor necrosis factor inhibitors [TNFi]) may be initiated. Both a non-biologic DMARD and biologic DMARD may be initiated early in the disease course for severe, vision-threatening complications, rather than non-biologic DMARD monotherapy.[21]

Methotrexate (MTX) is the first-line, non-biologic DMARD used to treat NIU, and it is preferred for its efficacy, safety, and tolerability. Estimates of the proportion of patients with NIU treated with MTX range from 45%[22] to 85%.[23] Nevertheless, MTX treatment has been estimated to fail as monotherapy in at least a third of patients;[24] other estimates of failure exceed 50%.[25,26] In addition, it can take at least 3-4 months[27] for MTX treatment to have full effect during which time children remain at risk of incurring additional complications such as cataract or glaucoma from ongoing inflammation or concurrent corticosteroid use. Characteristics of children likely to fail MTX and require biologic DMARD therapy and whether earlier initiation of biologic therapy might confer greater treatment benefit are unknown.

1.6 Visual Acuity Outcomes and Complications

Even with aggressive treatment, the frequency of vision loss and ocular complications remains high. There are few reliable estimates but some from larger studies are summarized below.

Table 1 – Visual Acuity Data from Larger Studies:

	Smith et al[8] (n=527 eyes baseline; n=63 eyes at 3 yrs; n=22 at 5 yrs; n=13 at 10 yrs)	**Kump et al[15] n=469 eyes**	**Tekin et al[23] n=83 eyes**	**Gregory et al[28] N=596 eyes[a]**	**Markomichelakis et al[29] (n=533 eyes at baseline; n=315 eyes at 2 yrs; n=283 eyes at 3 yrs; n= 230 at 5 yrs)**
VA 20/50 or worse	21% at 3 yrs 36% at 5 yrs 31% at 10 yrs	17% at last follow-up		43% (best eye) at last follow-up	3.5% at 2 yrs 3.6% at 3 yrs 5.6% at 5 yrs
VA 20/200 or worse	3% at 3 yrs 15% at 5 yrs 8% at 10 yrs	5%[a] at last follow-up *Worse than 20/200*	1% at last follow-up *20/400 or worse*	27% (best eye) at last follow-up	4.7% at 2 yrs 4.3% at 3 yrs 5.9% at 5 yrs
Length of Follow-up	Median 3 yrs (range: 1 to 10 yrs)	Median 22 months (range 1 day to 221 months)	Median 49 months (range 6 to 141 months)	Median 2.62 yrs (range 0-24 yrs)	Median 30 months (range, 6–82 months)

[a] All JIA

Table 2 - Complication Data from Larger Studies:

	Ferrara et al[9] N=520 eyes	**Kump et al[15] N=469 eyes**	**Smith et al[8] N=926 eyes** *(rate at 3 yrs)*	**Dajee et al[30] N=68 eyes**	**Gregory et al[28] N=596 eyes[b]**
Glaucoma	121 (23%)	71 (15%)	7 (11%)	11 (16%)	86/281 (31%)
Cataract	228 (44%)	188 (40%)	31 (49%)	18 (26%)	--
Posterior synechiae	102 (20%)	164 (35%)	30 (48%)	16 (24%)	69/232 (30%)
Band keratopathy	70 (13%)	107 (23%)	29 (46%)	9 (13%)	79/220 (36%)
Optic nerve involvement	108 (21%)	38 (8%)	--	--	--
Maculopathy	111 (21%)	111 (24%)	15 (24%)	2 (3%)	38/309 (12%)
Retinal detachment	14 (3%)	14 (3%)	--	3 (4%)	--
Hypotony	Not reported	18 (4%)	6 (10%)	--	44/314 (14%)
Follow-up	Min 5 months	Median 22 months (range 1 day to 221 months)	Median 3 yrs (range: 1-10 yrs)	Median 13.5 months	Median 2.62 yrs (range 0-24 yrs)

[b] All JIA

1.7 Rationale for Present Study

Despite advances in diagnosis and treatment, poor visual outcomes remain prevalent in children with uveitis, not only from the disease process itself, but from corticosteroid-related side effects. Therefore, there is a pressing need for a multicenter data collection study as proposed, to identify the clinical features and prevalence of the types of uveitis in children. Collecting such data will help design future randomized clinical trials to evaluate treatments for children with uveitis.

Key study aims include defining specific uveitis phenotypes and etiologies and providing data on the types of current and past treatments prescribed. Another important aim is to develop a comprehensive Rasch-analyzed PEDIG Uveitis QoL questionnaire for use in future uveitis studies.

1.8 Study Objective

Over a one-year period, to enroll children diagnosed with uveitis and collect data regarding clinical features and current and past treatments at time of enrollment. For children with new onset non-infectious uveitis (onset within 6 months prior to enrollment), a medical record review will collect data 12-months after enrollment.

1.8.1 Specific Aims

The specific aims of this observational study are to:

1. Describe the frequency of uveitis subtypes in children <18 years of age, including new onset uveitis (<6 months duration).
2. Describe clinical and demographic characteristics overall and within each type of uveitis.
3. Compare characteristics between uveitis subtypes.
4. Describe current and previous treatment history by type of uveitis.
5. Describe clinical measures done as part of usual care.
6. Determine recruitment potential overall and by site for different disease sub-types (new-onset vs. established disease, localization, etiology) for future randomized clinical trials.
7. Evaluate relationships between demographic, treatment, and clinical characteristics and quality of life as measured by the EYE-Q (current version) questionnaire.
8. Develop a comprehensive PEDIG Uveitis Quality of Life questionnaire by administration and calibration of EYE-Q plus additional uveitis-specific and treatment related items.

1.9 Potential Risks and Benefits

This is an observational data-collection study in children with uveitis. Participants with uveitis will be enrolled and managed according to the investigator's usual clinical practice. Current clinical data and past historical data will be collected from chart review after informed consent and again 12-months after enrollment for children with new onset non-infectious uveitis (onset within 6 months of enrollment).

1.9.1 Known Potential Risks

The risk to participating participants is the unlikely event of sensitive personal health information being viewed by an unauthorized person. Efforts are being made to ensure that this does not occur, as described in Chapter 7.

1.9.2 Known Potential Benefits

There are no direct benefits for study participants. Results of this study will provide important new knowledge that will be helpful to design future randomized trials in children less than 18 years of age with uveitis.

1.10 Risk Assessment

The protocol's level of risk is consistent with 45 CFR 46.404 and 21 CFR 50.51, which indicates research not involving greater than minimal risk for the individual involved in the research.

1.11 General Considerations

The study is being conducted in compliance with the policies described in the network policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Chapter 2: Study Enrollment

2.1 Participant Recruitment and Enrollment

The study plans to enroll up to 300 participants over a one-year recruitment period for whom parental informed consent and child assent will be obtained.

Study participants will be recruited from PEDIG clinical sites and clinical sites affiliated with the American Uveitis Society (AUS). All eligible participants will be included regardless of sex, race, or ethnicity. There is no restriction on the number of participants enrolled at each site.

As the study approaches the end of enrollment, sites will be notified of the end date for recruitment into the study. Participants who have signed informed consent forms can be enrolled until the end date.

A screening log will be kept of all participants eligible for inclusion but not enrolled, along with the reason for not enrolling.

2.1.1 Informed Consent

A child is considered for the study after undergoing a routine eye examination (i.e., as part of usual care) that identifies uveitis appearing to meet the eligibility criteria. The study will be discussed with the child's parent(s) or guardian(s) (referred to subsequently as parent(s)).

Parent(s) and children 13 years of age or older who express an interest in the study will be given a copy of the informed consent form to read.

Prior to performing any study-specific procedures that are not part of the child's routine care, written or electronic informed consent must be obtained from the parent and child if the child is 13 years of age and older; and child assent must be obtained from a child 7 years of age and older but less than 13 years of age.

If informed consent and assent if required cannot be obtained, then study data collection cannot continue.

If the participant and/or parents are not fluent in written and spoken English, then the consent and/or assent forms must be translated into a language of fluency for the participant/parent. Further, a qualified interpreter must be available for the consent process and all subsequent study-related interactions.

A child is considered enrolled when the informed consent form and assent form (as applicable) have been signed.

2.2 Eligibility Criteria

2.2.1 Participant Inclusion Criteria

Individuals must meet all the following inclusion criteria to be eligible:

- Age:
  - Incident cases (onset ≤ 6 months) <17 years
  - Established cases (onset > 6 months) <18 years
- Diagnosis of any type of uveitis (infectious or noninfectious) in any location except traumatic and post-operative uveitis.
- Active or inactive uveitis with any treatment status (current / prior / none [but under surveillance]).

2.2.2 Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation:

- Bilateral uveitis with differing etiologies
- Traumatic uveitis
- Post-operative uveitis
- Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is an investigative site personnel directly affiliated with this study or who is an employee of JAEB Center for Health Research.
- Ocular disease related to Retinoblastoma, Coat's disease, retinitis pigmentosa, inherited retinal degeneration, Juvenile xanthogranuloma (JXG), or leukemia/malignancy within the eye.

2.3 Screening Procedures

After signed informed consent (and assent, if required), a potential participant will be evaluated for study eligibility by reviewing their medical history, along with data collection and clinical testing as below.

2.3.1 Demographic and Historical Information

The following demographic and historical information will be collected either as part of the clinical exam or by review of available medical records and by parental / patient interview:

1. Age at enrollment
2. Sex
3. Race / ethnicity
4. Age at initial diagnosis
5. Weight: estimated by parent or as noted in the medical record
6. Socioeconomic factors: distance from care, socioeconomic status, highest parental education, insurance status (private, uninsured, government)
7. Ocular and medical history:
   a. Prior medical treatments
   b. Current medical treatments
      i. Current systemic treatment dose and frequency
      ii. Current eye-drop type +/- frequency
   c. Prior surgeries
   d. Complications and diagnoses

2.3.2 Systemic Disease

Current systemic diagnoses will be recorded and will include juvenile idiopathic arthritis, sarcoidosis, Behcet disease, Vogt-Koyanagi-Harada, Tubulointerstitial Nephritis and Uveitis syndrome, Inflammatory bowel disease, *NOD2*-spectrum syndrome, and other autoimmune and/or infectious conditions.

2.3.3 Clinical Testing

Clinical Measures:

1. Monocular Distance Best Corrected Visual Acuity
   In each eye, using investigators usual method, noting method.

2. Intraocular Pressure
   In each eye (mmHg), noting method (iCare, applanation, tonopen).

3. Pupillary Reaction
   Including recording of whether an afferent pupillary defect is present in each eye.

4. Slit Lamp Exam
   Including evaluation of the cornea, iris, lens, anterior chamber, and posterior segment. Grading of cell count and flare pre-dilation using SUN criteria[1] (see section 2.5.5).

5. Dilated Fundus Exam

   a. Slit lamp exam by investigators usual method:
      i. Grading of vitreous cell post-dilation as described in the MUST trial[31] (see section 2.5.6)
      ii. Assessment of the retina with careful attention to the macula and optic nerve

   b. Indirect ophthalmoscopy:
      i. Grading of vitreous haze as described by Nussenblatt et al[32] and adopted by the SUN group[1] (see section 2.5.6).
      ii. Assessment of the peripheral retina with scleral depressed exam if indicated/tolerated

Other clinical testing, performed according to the investigator's usual practice (if done as usual care), will also be collected if performed at the time of enrollment or within 60 days prior to enrollment:

6. Ocular Alignment
   Presence versus absence of manifest strabismus at distance or near with designation of the principal direction (esotropia, exotropia, or hypertropia). Measurement of strabismus magnitude (if strabismus present) is not required.

7. Refraction

Investigators preferred method with cycloplegia.

To help understand what constitutes usual care, investigators will be asked to indicate whether the following specific tests were performed, but test data will not be collected:

- Slit lamp photography
- Electroretinogram
- Visual fields
- Fluorescein angiography
- Optical coherence tomography of the optic nerve
- Optical coherence tomography of the macula
- Anterior segment OCT
- Magnetic resonance imaging
- Ultrasound (UBM)
- Ultrasound (B-scan)
- Indocyanine green angiography
- Color or pseudocolor fundus images
- Fundus autofluorescence
- A-scan (axial length for glaucoma)

2.4 Questionnaires

At the time of enrollment, the EYE-Q plus additional uveitis-specific quality of life and treatment questions (identified from a literature review) may be completed by children age 8 to <18 years; parent proxy may be completed by one parent for each child <18 years; parent questionnaires may be completed by one parent for each child <18 years.

2.4.1 Questionnaire Administration

For each participant, questionnaires should be attempted to be completed while the patient is in office. Questionnaires will be administered electronically with a login for each participant. For child questionnaires, the questionnaire MUST be completed during the visit and cannot be continued out of the office. For both the proxy and parent questionnaires, questionnaires may be completed after the visit, as long as completed within 7 days of the enrollment visit.

2.5 Uveitis Classification

For each participant clinical and historical data will be used to record the following for each affected eye: etiology, localization, course, activity, control, and complications.

2.5.1 Etiology

Uveitis will be classified as either non-infectious or infectious. Cause (suspected or confirmed) will be recorded as indicated on study data collection forms, grouping in the following broad categories:

- Non-infectious:
  - JIA-associated
  - other systemic
  - undifferentiated

- other
- Infectious
- Drug-induced
- Other

2.5.2 Localization

Localization will be classified as bilateral vs unilateral and using the SUN criteria[1] as follows:

- *Anterior* (anterior chamber): includes iritis, iridocyclitis, anterior cyclitis
- *Intermediate* (vitreous): pars planitis, posterior cyclitis, hyalitis
- *Anterior and intermediate*
- *Posterior* (retina or choroid): focal, multifocal or diffuse chorioretinitis, chorioretinitis, retinochoroiditis, retinitis, neuroretinitis
- *Panuveitis*: anterior chamber, vitreous and retina or choroid

2.5.3 Disease Course

Disease course will be classified in accordance with the SUN criteria:[1]

- Acute: episode characterized by sudden onset and limited (≤3 months) duration
- Chronic: persistent uveitis with relapse <3 months after discontinuing treatment
- Recurrent: repeated episodes separated by periods of inactivity without treatment for ≥3 months.

2.5.4 Disease Duration

'New-onset' cases will have less than 6 months total duration of disease.

2.5.5 Disease Activity – Anterior Chamber

Disease activity will be graded in accordance with the SUN criteria[1]

Grading system for anterior chamber cells[1]

Grade	Cells in field†
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

† Field size is 1mm x 1mm slit beam

Grading system for anterior chamber flare[1]

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens detail clear)
3+	Marked (iris and lens detail hazy)
4+	Intense (fibrin or plastic aqueous)

2.5.6 Disease Activity – Vitreous

Grading system for vitreous haze[32] through indirect ophthalmology

Grade	Description
0	None
0.5	Slight blurring of optic disc margin; normal striations and reflex of the nerve fiber layer cannot be visualized
1+	Obscured view with definition to the optic nerve head and retinal vessels
2+	Obscured view with definition to the retinal vessels
3+	Optic nerve head visualized, but with blurry borders
4+	Obscured fundal view

Grading system for vitreous cell[31]

Grade	Cells in field†+
0	No cells
0.5/Trace	1 to 5 cells
1+	6 to 10 cells
2+	11 through 20 cells
3+	21 through 50 cells
4+	51 or more cells

† Field size is 1mm x 0.5mm slit beam
+Grade is based on number of cells in syneretic spaces
As assessed post-dilation at the slit lamp

2.5.7 Disease Control

For each affected eye, uveitis control will be classified as either:

1. Full control
   - Grade 0 AC cell
   - Grade 0 vitreous haze
   - No retinal / choroidal inflammation
   - If FA performed, no vascular leakage posterior to the equator

2. Minimal activity
   - <=0.5+ AC cell
   - Grade 0 vitreous haze
   - No retinal / choroidal inflammation
   - If FA performed, no vascular leakage posterior to the equator

3. Uncontrolled
   - Criteria for full control or minimal activity are not met.

If criteria for either full control or minimal activity are met, further classification will be made regarding the use of topical or oral steroids:

- *Steroid-free:* no systemic or topical steroids being used. No peri/intraocular steroid injections for 6 months.

- *Steroid-limited:* Topical steroids (prednisolone acetate 1%, or equal to/less potent equivalent) - no more than 2 drops / day and no systemic steroids. No peri/intraocular steroid injections for 3 months
- *Steroid-dependent:* does not meet criteria for steroid-free or steroid-safe control
- *Remission:* full control with no topical or systemic medications of any kind for ≥3 months with no disease activity

2.5.8 Ocular Complications

Specific complications present at the time of the enrollment ocular exam will be recorded including cataract, ocular hypertension, glaucoma, optic disc edema, band keratopathy, hypotony, epiretinal membrane, posterior synechiae, and cystoid macular edema.

The presence of glaucoma and glaucoma suspect will be defined according to Childhood Glaucoma Research Network (CGRN) criteria[33]:

- Glaucoma: presence of ≥2 of the following: 1) Intraocular pressure (IOP) of greater than 21 *mmHg*, 2) optic nerve glaucomatous damage such as increased cupping, focal notching, or cup to disc asymmetry of 0.2 or more between both eyes, 3) visual field defects consistent with optic nerve glaucomatous damage 4) Myopic shift or increased axial length

- Glaucoma suspect: one of the following: presence of ocular hypertension (IOP of greater than 21 mmHg; IOP elevation must be reproducible), visual field abnormalities suspicious of glaucoma, optic nerve appearance suspicious of glaucoma, or signs of ocular enlargement (e.g., increased corneal diameter or axial length) with normal IOP.

2.6 Treatment

Participants will be managed according to the investigator's usual clinical practice. Documentation of current and prior treatment will include dose and frequency of each.

2.7 Medical Record Review

There is no study-mandated follow-up visit schedule, and no protocol related to how patients should be managed. Visits occur as part of standard patient care. For children with new onset non-infectious uveitis (onset within 6 months prior to enrollment), data will be collected 12-months following enrollment from standard care visits (visit window Enrollment +11 months to Enrollment +15 months). When applicable, if more than one element is available for a report field, the most recent element will be reported.

Data collected will mirror data collection at time of enrollment and is summarized in the Study Procedures Table.

Chapter 3: Unanticipated Problem / Adverse Event Reporting

3.1 Unanticipated Problems

Given that the study is cross-sectional with data collection only, unanticipated problems are not expected. However, if an unanticipated problem meeting the criteria below does occur, site investigators will promptly report it to the Coordinating Center on an eCRF within seven (7) calendar day of recognition. An unanticipated problem is an incident, experience, or outcome that meets all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the Coordinating Center or at another participating entity such as a pharmacy or laboratory.

These instances must be reported to the JCHR IRB within seven calendar days of recognition.

The Director of the Human Research Protection Program will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem that requires further reporting.

3.2 Adverse Events

The study is a passive data collection study and includes no specific intervention or use of a device or drug as part of the protocol. Some participants may receive treatment for uveitis and some may not. Data from any complications from past treatments will be collected at investigator discretion but are not considered adverse events.

The Coordinating Center will not be conducting any on-site monitoring.

3.3 Stopping Criteria

The study may be discontinued by the Jaeb Center for Health Research at any time.

Chapter 4: Miscellaneous Considerations

4.1 Contacts by the Jaeb Center for Health Research and Sites

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will NOT be provided with the parent's contact information and will not contact the parents or participant.

4.2 Participant Compensation

Participant compensation will be specified in the informed consent form.

4.3 Participant Withdrawal

Data will be collected at a single point in time after informed consent and assent if required. Participation in the study is voluntary.

4.4 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

In addition, to help identify the study participant, the informed consent form and the assent form (if applicable) will include permission for the PEDIG Coordinating Center to receive the child's initials (first, middle, and last name initial).

Study data will be entered on the Coordinating Center's secure website through an SSL encrypted connection. The Coordinating Center websites are maintained on Unix and Linux servers running Apache web server software and on a Windows server running IIS, all with strong encryption. The registry website is password-protected and restricted to users who have been authorized by the Coordinating Center to gain access. No identifiable health information of an enrolled participant will be released by the Coordinating Center.

Chapter 5: Statistical Considerations

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan (SAP) will be written and finalized before the first enrollment.

5.1 Sample Size

Up to 300 children will be enrolled over a one-year period. This sample is chosen for convenience and not based on statistical principles. To provide estimates of precision, **Table 3** below shows the expected half-width for a 95% confidence interval for various sample sizes and proportions. Note that the half-width for 60% is identical to 40% and so-on.

Table 3. Half-Width Table for Proportions

Sample Size	Sample Proportion				
	10%	20%	30%	40%	50%
100	6%	8%	9%	10%	10%
150	5%	6%	7%	8%	8%
200	4%	6%	6%	7%	7%
250	4%	5%	6%	6%	6%
300	3%	5%	5%	6%	6%

5.2 Primary Analysis

There is not a formal primary analysis for this study. There are 8 specific aims (see Section 1.8.1) related to demographic and clinical characteristics, recruitment potential, and quality of life that will be addressed.

5.3 Descriptive Data (Specific Aims 1–5)

The following data will be summarized overall and by uveitis subtype/etiology (Section 2.5) at enrollment and following 12-month chart review.

- Demographic and historical information (see Section 2.3.1)
- Socioeconomic factors
- Laterality at time of initial diagnosis and at time of enrollment (if not diagnosed at time of enrollment)
- Presence of systemic disease (see Section 2.3.2)
- Clinical testing (see Section 2.3.3)
- Etiology (see Section 2.5.1)
- Localization per the SUN criteria[1] (see Section 2.5.2)
- Disease course classified per the SUN criteria[1] (see Section 2.5.3)
- Disease Duration (Section 2.5.4):
  - *New onset*: onset less than 6 months prior
  - *Established:* present for 6 months or more
- Disease Activity
  - Anterior chamber cells and flare per the SUN criteria[1] (see Section 2.5.5)
  - Vitreous haze and vitreous cell (see Section 2.5.6)
- Disease Control (see Section 2.5.7)

- Ocular complications (see Section 2.5.8)
- Current and past treatments (see Section 2.6)

5.4 Recruitment potential (Specific Aim 6)

Total and monthly recruitment will be tabulated overall and stratified by site and type of uveitis.

5.5 Questionnaires (Specific Aims 7-8)

Responses to all questionnaire items (EYE-Q as well as additional items) from each of the 3 questionnaires (child, proxy, and parent) will be used to create scores for analysis. For each score, univariate relationships with each factor in Section 5.3 will be evaluated using linear regression. To address the risk of false positives due to multiple comparisons, the false discovery rate (FDR) will be controlled at 5%. Results will be considered significant if the FDR-adjusted p-value is < 0.05.

5.5.1 Rasch Analysis

Existing EYE-Q items will be combined with uveitis-specific quality of life questions. The child, proxy, and parent responses will be used in separate factor analyses to determine the number of domains for each questionnaire. Each domain will be refined through the evaluation of misfitting items and will then be Rasch scored.

5.5.2 Missing Data

In the event of missing data, a complete case analysis will be conducted unless otherwise specified in the SAP. The potential impact of missing data will be assessed, and sensitivity analyses may be conducted as appropriate.

Chapter 6: Data Collection and Monitoring

6.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live participant must be recorded (e.g., office note, visit record, etc.).

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

6.2 Study Records Retention

Study documents should be retained for a minimum of 3 years after completion of the final grant reporting. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

6.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol adhering to Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable.

The Coordinating Center will not be conducting any on-site monitoring.

6.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site PI/study staff are responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 7: Ethics/Protection of Human Participants

7.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

7.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

7.3 Informed Consent Process

7.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their parents or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

7.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records

required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

When feasible, data will be directly collected in electronic case report forms, which will be considered the source data. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Jaeb Center for Health Research staff will be secured and password protected.

At the end of the study, all study databases will be de-identified and archived at the Jaeb Center for Health Research.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

7.5 Future Use of Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. After the study is completed, the de-identified, archived data will be made available to the public.

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