PEDIATRIC UVEITIS STUDY
(UV1)

A Study of Uveitis in Children <18 Years of Age

Statistical Analysis Plan

Effective date: 28 April 2026

NCT07518134

Version History

This SAP was written with reference to protocol version 1.2. If the protocol is subsequently updated, then this SAP will be reviewed to ensure consistency with the new protocol. The SAP will not be revised unless the protocol changes require modification of the analyses.

Version	Protocol Version	Author	Approver	Effective Date	Study Stage
1.0	1.2	Yufeng Zhu	Wesley Beaulieu	28 Apr 2026	First participants have been enrolled. Data have not been reviewed or analyzed.

Version	Revision Description
1.0	Original Version

Approvals

Role	Digital Signature or Handwritten Signature/Date
Author (Statistician)	Yufeng Zhu I am the author of this document 2026.04.29 08:41:49-04'00'
Approver (Senior Statistician)	Wesley Beaulieu I am approving this document 2026.04.29 09:10:55-04'00'

1 Study Overview

The UV01 study will enroll children < 18 years old 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. The study protocol outlines 8 specific aims:

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.

The following sections describe the analyses to address each of the specific aims.

2 Consistency with the Protocol

The author of this document has confirmed the analyses described here are consistent with the version of the protocol indicated on the version history page.

Should there be any further discrepancy between the associated protocol and this SAP, the content of the SAP shall prevail.

3 Describe Cohort Overall and within Each Type of Uveitis

3.1 Objective

This section addresses the specific aims #1–5 the study protocol.

3.2 Tabulations

Tabulations will be created for the entire cohort and stratified by type of uveitis and new onset uveitis unless otherwise indicated. Tabulations will be repeated at 12 months for new-onset, non-infectious cases.

3.2.1 Participant-level uveitis clinical characteristics

- Uveitis Type
    a. Non-Infectious
        i. Uveitis Associated with Systemic Disease
            1. JIA-associated
            2. Other systemic associated
    b. Infectious
    c. Undifferentiated (idiopathic)
    d. Drug-Induced
- Uveitis course
    a. Acute
    b. Chronic
    c. Recurrent
- Laterality
- Localization of uveitis (SUN)*
    a. Anterior
    b. Intermediate
    c. Anterior and Intermediate
    d. Posterior
    e. Panuveitis
- New onset within the past 6 months

* If a bilateral participant has different localizations in each eye, the more posterior localization will be used for tabulation. Panuveitis will be considered the most posterior localization.

3.2.2 Participant-level demographic characteristics and medical/social history

- Sex
- Race
- Ethnicity
- Age at Enrollment
- Age at Uveitis Diagnosis
- Country of Birth
- Early feeding
- Parent Education Level
- Insurance
- History of smoking
- Home Location
- Social Vulnerability Index
- Other Current Ocular Diagnoses
    - Amblyopia
    - Manifest strabismus

3.2.3 Eye-level clinical characteristics

Clinical Testing

- Best Corrected Visual Acuity
- If abnormal, reason for reduced vision

Slit Lamp Exam

- Entirely normal
- Cornea
    - Normal
    - Band Keratopathy
    - Active Keratic Precipitates
    - Other
- Iris
    - Normal
    - Anterior Synechiae
    - Posterior Synechiae
    - Other
- Localization of uveitis (SUN)
    - Anterior
    - Intermediate
    - Anterior and Intermediate
    - Posterior
    - Panuveitis
- Anterior chamber
    - Cell grade
        - 0/0.5+/1+/2+/3+/4+
    - Flare
        - 0/1+/2+/3+/4+
- Lens
    - Normal
    - Cataract
    - Other
- Disease activity – vitreous
    - Haze
        - 0/0.5+/1+/2+/3+/4+
    - Cell grade
        - 0/0.5+/1+/2+/3+/4+
- Optic Nerve
    - Cup to disc ratio (continuous)
    - Edema present
    - Other
- Macula

    - Normal
    - Scarring
    - Epiretinal membrane (ERM)
    - Cystoid macular edema (CME)
    - Choroidal neovascular membrane (CNVM)
    - Vitreomacular traction (VMT)
    - Diffuse thickening (edema)
    - Subretinal fluid (SRF)
    - Macular atrophy
    - Other
- Vasculature
    - Normal
    - Sheathing
    - Occlusion
    - Leakage
    - Other
- Peripheral Retina
    - Normal
    - Retinal Hemorrhages
    - Chorioretinal scarring
    - Choroid or retinal infiltrates
    - Other
- Intraocular pressure (continuous)
- Method of measure intraocular pressure
    - Icare
    - Applanate
    - Tonopen
- Glaucoma/glaucoma suspect
    - Definite glaucoma
    - Glaucoma suspect
    - None
    - Unknown
- Angle closure > 50% (Yes or No)

Uveitis Control

- Current uveitis control
    - Full control
    - Minimal activity
    - Uncontrolled
- Current steroid use
    - Steroid-free control
    - Steroid-limited control
    - Steroid-dependent control

- Remission

Prior Surgery and Complications

- Cataract surgery
  - Aphakic
  - IOL implantation
    - Primary
    - Secondary
- Other surgery
- Prior ocular complications
- Glaucoma
  - Definite
  - Suspect
  - None
  - Unknown
- Glaucoma surgery
- Band keratopathy
- Synechiae
  - Peripheral anterior
  - Posterior
  - Unknown type
- Cataract
- Hypotony (IOP ≤ 5mm Hg)
- Optic disc edema
- Cystoid macular edema
- Epiretinal membrane formation
- Vasculitis / vascular leakage
- Other complication
  - Vitreous hemorrhage
  - Chorioretinal scare
  - Macular atrophy
  - Choroidal neovascular membrane
  - Retinal detachment
  - Retinal hole
  - Retinal tear
  - Vasoproliferative tumor
  - Optic atrophy
  - Phthisis
  - Other

Refraction (if completed)

- Spherical equivalent (continuous)
- Cylinder (continuous)

3.2.4 Participant-level treatment history

- Any prior systemic treatment (Yes or No)
    - Any prior systemic corticosteroid treatment (Yes or No)
        - Duration
        - Route
            - Oral
            - IV
            - Subcutaneous
    - Prescriber
        - Pediatrician
        - Rheumatologist
        - Ophthalmologist
        - Other
        - Unknown
- Prior Non-biologic DMARD (Yes or No)
    - MTX
        - Route
            - Oral
            - SQ
            - Unknown
        - Duration
        - Max dose
    - Mycophenolate (mycophenolate mofetil (Cellcept) or mycophenolic acid (Myfortic) or Unknown form)
        - Frequency
            - BID
            - Other
            - Unknown
        - Duration
    - Leflunomide (Arava)
        - Duration
    - Other
        - Route
        - Duration
        - Other
- Prior biologic
    - Adalimumab/biosimilar (Humira)
        - Dose
        - Duration
        - Frequency
    - Infliximab/biosimilar IV

        - Frequency
        - Duration
        - Max dose
    - Golimumab
        - Infusion
            - Dose
            - Duration
            - Frequency
        - Subcutaneous injection
            - Dose
            - Duration
            - Frequency
    - Certolizumab (subcutaneous injection)
    - Etanercept injection
    - Tocilizumab (Actemra)/biosimilar
        - Infusion
            - Max dose
            - Duration
            - Frequency
        - Subcutaneous injection
            - Max dose
            - Duration
            - Frequency
    - Abatacept
        - Infusion
        - Subcutaneous injection
        - Unknown route
    - Rituximab/biosimilar infusion
    - Janus kinase inhibitors (JAKi)
        - Tofacitinib
            - Max dose
            - Duration
        - Baracticinib
            - Max dose
            - Duration
        - Upadacitinib
            - Max dose
            - Duration
        - Unknown JAKi
            - Max dose
            - Duration

- Other
- Two or more systemic steroid-sparing IMTs used at one time
  - Yes
  - No
  - Unknown

3.2.5 Eye-level treatment history

- Any topical treatment
- Topical corticosteroid
  - Difluprednate
  - Prednisolone acetate 1%
  - Dexamethasone
  - Fluorometholone
  - Loteprednol
- Prior glaucoma drops
- Prior periocular/intraocular corticosteroid injection

3.2.6 Participant-level etiology for non-infectious uveitis

- ANA Status
- HLA-B27 Status
- JIA
  a. Oligoarthritis persistent
  b. Oligoarthritis extended
  c. Polyarthritis RF negative
  d. Polyarthritis RF positive
  e. Psoriatic
  f. Enthesitis
  g. Undifferentiated
  h. Unknown
- Sarcoidosis
- Adamantiades-Behcet's Disease
- Vogt-Koyanagi-Harada Disease
- Tubulointerstitial Nephritis and Uveitis
- Inflammatory bowel disease
- Blau Syndrome or Early-onset Sarcoidosis
- Eczema / atopy (Yes or No)
- Other autoimmune conditions (Yes or No)

3.2.7 Participant-level etiology for infectious uveitis

- Herpes Simplex Virus (HSV)
- Varicella Zoster Virus (VZV)
- Cytomegalovirus (CMV)
- Other Viral

- Toxoplasmosis
- Toxocariasis
- Histoplasmosis
- Tuberculosis
- Bartonella
- Diffuse Unilateral Subacute Neuroretinitis (DUSN)
- Syphilis
- Lyme
- Rubella
- Other microbe

3.2.8 Participant-level current medication use

- Corticosteroid
    - Oral
    - IV
- Non-biologic DMARD
    - MTX – Oral
    - MTX – Subcutaneous
    - Mycophenolate mofetil (Cellcept)
    - Mycophenolic acid (Myfortic)
    - Leflunomide (Arava)
    - Azathioprine – Oral
    - Azathioprine – IV
    - Cyclosporine – Oral
    - Cyclosporine – IV
    - Tacrolimus – Oral
    - Tacrolimus – IV
    - Other – Oral
    - Other – IV
- Biologic
    - Adalimumab (Humira)
    - Adalimumab (Humira) – Biosimilar
    - Infliximab IV
    - Infliximab IV – Biosimilar
    - Golimumab – infusion
    - Golimumab – subcutaneous injection
    - Certolizumab
    - Etanercept
    - Tocilizumab (Actemra) or Biosimilar – Infusion
    - Tocilizumab (Actemra) or Biosimilar – Injection
    - Abatacept – Infusion
    - Abatacept – Injection
    - Rituximab infusion

- Tofacitinib – Immediate release
- Tofacitinib – Extended release
- Baracticinib
- Upadacitinib
- Other

3.2.9 Eye-level current medication use

- Any topical treatment
- Topical non-steroid
  - Non-cycloplegic
  - Cycloplegic
    - Tropicamide
    - Cyclopentalate
    - Atropine
    - Other
- Any glaucoma medication
- Topical glaucoma medication
  - Beta blockers
  - Alpha-2 agonists
  - Prostaglandin analogs
  - Rho kinase inhibitors
  - Carbonic anhydrase inhibitors
- Oral glaucoma medication (carbonic anhydrase inhibitors)
- Topical corticosteroid
  - Difluprednate
  - Prednisolone acetate 1%
  - Dexamethasone
  - Fluorometholone
  - Loteprednol
  - Other

3.2.10 Ancillary testing completed

- Fluorescein angiogram
  - Oral
  - IV
- Optical coherence tomography angiography (OCTA)
- Optical coherence tomography (OCT)
  - Anterior segment
  - Optic nerve
  - Retina/Macula
- Ultrasound
  - UBM

    - B-scan
- Brain MRI
- Indocyanine Green angiography
- Fundus Autofluorescence
- Color Fundus Photographs
- Visual Field
- Electroretinogram
- A-scan (axial length for glaucoma)
- Slit lamp photography

3.2.11 Treatment prescribed

- Treatment change being made
- Specific change(s)
    - Current medication discontinued
    - Current medication changed frequency
    - Current medication changed dose
    - New medication started
- Reason(s) for change(s)
    - Uncontrolled
    - Incomplete control
    - Steroid dependence
    - Complication(s)
    - No longer needed
    - Weaning
    - Nonadherence
    - Insurance access
    - Side effects

4 Recruitment Potential

4.1 Objective

The objective of this aim is to determine recruitment potential overall and by site for different disease sub-types (new-onset vs. established disease, localization, etiology) for future randomized clinical trials (specific aim #6 in study protocol).

4.2 Tabulations

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

5 Vision-related quality of life and visual function (EYE-Q)

5.1 Objective

The objective of this aim is to evaluate relationships between demographic, treatment, and clinical characteristics and quality of life as measured by the EYE-Q questionnaire (specific aim #7 in study protocol).

5.2 Background

At the time of enrollment, the EYE-Q plus additional uveitis-specific quality of life and treatment questions that measures vision related functioning (VRF) and vision related quality of life (VRQoL) will be completed by children age 8 to <18 years; parent and proxy questionnaires will be completed by one parent for each child <18 years. **Only the original child and proxy EYE-Q questions will be used for this specific objective.**

The child and proxy questionnaires use a 3-point response scale that measures the difficulty in completing VRF tasks and how true a QoL statement is (0 = never, 1 = sometimes, 2 = always). Domain scores range from 0 to 100, and higher scores indicate better VRQoL and/or VRF.

5.3 Calculation of the Scoring System

Scores will be calculated for Vision related functioning (VRF) and vision related quality of life (VRQoL) domains.

Vision related functioning (VRF) questions (from Cassedy et al.[1]):

1. It is hard to see the board if I am sitting in the back of the room.
2. It is hard to see the pictures on the television screen from across the room.
3. It is hard to see someone's facial expressions (smiling, frowning) when they are talking to me.
4. It is hard to see someone's face from across the room.
5. It is hard to see the words in my books if I am holding my book far from my face.
6. It is hard to see the steps so I do not trip when going up the stairs.
7. It is hard to see how much to fill a glass with a drink.
8. It is hard to see where to write on lined notebook paper.
9. It is hard adjusting to see where to sit when I walk into a dark room.
10. It is hard adjusting to see when I go from a dark room to a brightly lit room.
11. It is hard to see when I first walk outside into the sunlight.
12. It is hard to play sports that use small balls like in baseball, tennis, or golf.

13. It is hard to see the cursor on the computer screen.

14. It is hard to see words on a tablet or computer if I do not make the font larger in size.

15. It is hard to see text messages on a cellphone.

16.It is hard to do activities because of pain in my eyes.

Vision-related quality of life (VRQoL) questions:

1. I feel left out of activities because of my vision.

2. I do not join activities with friends because of my vision.

3. I do not like using eye drops.

4. I let my eye disease stop me from doing what I want to do.

5. I do not like getting injections or infusions for my eye disease.

6. I do not like having others know about my eye disease.

7. I get frustrated because I cannot do things because of my vision.

8. I do not like the way my eyes look.

Special aids question:

9. I use devices or special aids to help me see, such as:

    1. Large print books, cards, or games?

    2. Magnifying glass?

    3. Special lamps or lights?

    4.Other (not including glasses or contacts): _____

Steps to calculate the scores by each domain and total:

1. Reverse the score of each question. In the questionnaire, Never=0, Sometimes=1, Always=2. After reversing, Never=2, Sometimes=1, Always=0.
    - For Question 9 of VRQoL “I use devices or special aids to help me see”, there is no need to reverse the score. Points are deducted for visual aids because they are viewed as negatively impacting VRF and VRQoL.
2. Sum the score of all questions.

3. Divide the raw score by the number of questions answered except Question 9 from VRQoL (Special Aids).
4. Divide this average score by 2 to create a proportion, then multiply by 100 to get a percent score.
5. Truncate any negative scores to 0.

5.4 Quality of Life Outcomes

A total of 4 outcomes will be evaluated.

- Proxy (parents of all children, regardless of age)
    a. Visual-related function domain (VRF)
    b. Vision-related quality of life domain (VRQoL)
- Child (8 to <18 yrs)
    a. Visual-related function domain (VRF)
    b. Vision-related quality of life domain (VRQoL)Factors of Interest

The following factors will be evaluated for an association with any of the quality-of-life outcomes:

1. Age at diagnosis (continuous)
2. Best corrected visual acuity in the better-seeing eye (continuous)
    a. Hypothesis: Worse BCVA in the better-seeing eye will be associated with lower scores.[2,3]
3. Current treatment: Burden of topicals/Total drops per day (continuous)
    a. Hypothesis: Increased total drops per day will be associated with lower scores.
    b. Use the eye that has more total drops per day.
4. Localization (non-anterior vs anterior)
    a. Hypothesis: Non-anterior uveitis will be associated with lower scores.[4]
    b. If either eye has non-anterior uveitis, then the child will be classified as having non-anterior uveitis.
5. Presence of glaucoma or glaucoma suspect in current complications (binary: Y/N)
    a. Hypothesis: Presence of glaucoma or glaucoma suspect will be associated with lower scores.[5]
    b. If either eye has glaucoma or glaucoma suspect, then the child will be classified as having glaucoma or glaucoma suspect.
6. Presence of cystoid macular edema in current complications (binary: Y/N)
    a. Hypothesis: Presence of cystoid macular edema will be associated with lower scores.
    b. If either eye has cystoid macular edema, then the child will be classified as having cystoid macular edema.
7. Systemic disease etiology (3 levels: non-infectious uveitis not associated with systemic disease vs. non-infectious uveitis associated with systemic disease vs. other uveitis)
    a. Hypothesis: Non-infectious uveitis associated with systemic disease will be associated with lower scores.
8. Current systemic medications (binary: MTX vs non MTX)
    a. Hypothesis: MTX will be associated with lower scores.

    b. The systemic medications will be analyzed as binary, as few participants are expected to receive no treatment. If the size of the no treatment group is not negligible, then systemic medication may be modeled as a 3-level variable: MTX vs non MTX treatment vs. no treatment.
9. SVI (continuous)
    a. Hypothesis: Higher SVI will be associated with lower scores.
    b. The 5-digit zip code will be translated into an SVI score via the publicly available 2022 source data table. The dataset is available from https://www.atsdr.cdc.gov/place-health/php/svi/svi-data-documentation-download.html
10. Highest parental education (2 levels: Bachelor's degree or higher vs. Associates degree or lower)
    a. Hypothesis: Lower parental education will be associated with lower scores.
    b. If the number in either category is less than 20, then categories may be modified (e.g., Associate's or higher vs. some college or lower).
11. Disease control level (binary: Controlled [Full control and Minimal activity] vs uncontrolled)
    a. Hypothesis: Uncontrolled disease will be associated with lower scores.
    b. If disease in either eye is uncontrolled then the child will be categorized as uncontrolled.
12. Laterality of disease (unilateral vs bilateral)
    a. Hypothesis: participants with bilateral disease will have lower QoL.[2]

5.5 Analyses

At enrollment, responses to child and proxy questionnaire items by domains will be used to create outcome scores for analysis. For each outcome score, univariate relationships with each factor in Section 5.4 will be evaluated using linear regression. These univariable analyses are considered exploratory.

Assumptions of linearity, normality, and heteroscedasticity will be verified graphically. Continuous factors will be modeled using the continuous variable unless non-linearity is detected. In such a case, the factor may be categorized or transformed. If normality of residuals is seriously violated, data transformation, robust methods, or other approaches will be considered. Heteroscedasticity, if present, may be addressed by using a heteroscedasticity consistent variance estimator or data transformation.

Before evaluating multivariable main effect models, collinearity between each factor will be evaluated by calculating variance inflation factors (VIF). Any covariate with a VIF of 5 or higher will be considered possibly colinear and potentially excluded from or analyzed in separate multivariable models.

A multivariable model for each outcome will include each factor in Section b. The FDR will be controlled at 5% (see Section 5.6). The multivariable model will be considered the primary analysis for this specific aim.

Following evaluation of multivariable main effect models, two-way interaction terms will be explored in a sensitivity analysis. The main effects model will be considered primary. All possible 2-way interactions will be fit in separate models (including all main effects even

for factors not being tested in an interaction). The FDR for the interaction tests will be adjusted within separate families by outcome with the FDR controlled at 5% given the number of tests and anticipated low power for interactions.

Additional factors not listed in Section 5.4 will be investigated in separate exploratory analyses.

5.6 Multiplicity

The adaptive false discovery rate procedure of Benjamini, Hochberg, and Yekutieli[6] will be applied to control the false discovery rate at 5% for the primary analysis and 5% for the sensitivity analysis. The two-sided 95% confidence intervals for model effects and p-values will be adjusted. Each outcome (child and proxy questionnaire domains) will be treated as separate families of tests for adjustment (total of 4 families). Nominal P values and 95% confidence intervals may also be presented to aid in interpretation.

5.7 Missing Data

Missing data will be imputed using multiple imputation with 100 imputations. All factors in Section 5.4 will be included in the imputation model.

6 PEDIG Uveitis Quality of Life Questionnaire

6.1 Objective

Develop a comprehensive PEDIG Uveitis Quality of Life questionnaire by administration and calibration of EYE-Q plus additional uveitis-specific and treatment related items (specific aim #8 from study protocol).

6.2 Analyses

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. A separate analysis plan will be developed to further outline this process.

7 References

1. Cassedy A, Altaye M, Andringa J, et al. Assessing the Validity and Reliability of the Effects of Youngsters' Eyesight on Quality of Life Questionnaire Among Children With Uveitis. *Arthritis Care Res (Hoboken)*. 2022;74(3):355-363.
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5. Miraldi Utz V, Cassedy A, Aundhia M, et al. Clinical characteristics and quality of life measures in children with glaucoma-suspect or glaucoma diagnoses in chronic, noninfectious uveitis. *J AAPOS*. 2026:104804.
6. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*. 2006;93(3):491-507.