First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial

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First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial

Manual of Operations & Procedures

(MOP)

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Investigators, Personnel and Study Sites

Investigators, Personnel and Study Sites, continued.

[redacted]

Data Safety and Monitoring Committee (DSMC) Members

Background

In the First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial, we propose to establish which immunosuppressive therapy, methotrexate or mycophenolate mofetil, is more effective as a first-line, corticosteroid-sparing agent for the treatment of non-infectious uveitis. Uveitis, a set of conditions defined by intraocular inflammation, is a significant cause of vision loss and morbidity in the United States and the world.[1, 2] The incidence was recently estimated to be more than 50 cases per 100,000 person-years, with a prevalence of approximately 115 per 100,000 persons.[3] Additionally, uveitis is believed to be the cause of up to 10% of cases of legal blindness in the United States, or approximately 30,000 new cases of blindness per year.[1, 3, 4] In contrast to common age-related eye disorders, uveitis may have a stronger socio-economic impact because it disproportionately affects younger working-age patients.[5] Although the etiology of uveitis is varied, most cases are presumed to be immune-mediated and lack a known infectious cause.[6-9] Even in developing countries such as India that have a larger burden of infection, the vast majority of cases are non-infectious.[10, 11]

The current mainstay of treatment for non-infectious uveitis is corticosteroids (topical, systemic, locally injected, or corticosteroid-eluting implants). Due to the well documented local and systemic side effects associated with corticosteroid therapy, other immunosuppressive therapies are frequently used as corticosteroid-sparing agents in patients who need long-term therapy. These include antimetabolites, calcineurin inhibitors, alkylating agents, and biologic drugs.[12] Cost and morbidity associated with uncontrolled inflammation make the selection of an effective initial steroid-sparing agent extremely important.

When corticosteroid-sparing therapy is required, the two most commonly used first-line immunosuppressive agents are methotrexate and mycophenolate mofetil.[13] Because of cost and potentially dangerous long-term side effects, other classes of drugs such as biologics are typically reserved for refractory cases in which other treatments have failed.[12] It is common practice for patients requiring a steroid-sparing agent to be treated first with the less expensive methotrexate and then switched to mycophenolate mofetil in the event of treatment failure. However, results from non-comparative retrospective case series indicate that uveitis patients may be much more likely to achieve controlled inflammation and tolerate treatment with mycophenolate mofetil. [13-28] Furthermore, approximately half of the patients who fail treatment with methotrexate go on to successful treatment with mycophenolate mofetil.[29] Unlike in rheumatology, where clinical trials have demonstrated differential efficacy of antimetabolites for systemic inflammatory diseases, there have been no prospective randomized, controlled trials in uveitis to systematically determine which antimetabolite is more clinically efficacious as initial corticosteroid-sparing therapy. This makes it difficult for clinicians to make informed, evidence-based decisions about first-line immunosuppressive treatment. In addition, if patients fail one antimetabolite, there is no evidence basis for deciding whether to switch to another antimetabolite, or to move on to another class of immunosuppressives, including biologics.

1. Introduction to trial

The proposed study is a randomized comparative effectiveness trial to determine which treatment, methotrexate or mycophenolate mofetil, is more effective as first-line corticosteroid-sparing treatment for patients with non-infectious intermediate, posterior and panuveitis requiring corticosteroid-sparing therapy.

Two hundred sixteen patients with non-infectious uveitis in need of corticosteroid-sparing therapy will be randomized to receive either oral methotrexate or oral mycophenolate mofetil at [redacted] They will be followed monthly for 6 months after enrollment or until treatment failure. Patients who achieve success at 6 months will continue for another 6 months on the same medication. Patients who fail at 6 months will switch treatments and be followed for an additional 6 months or until failure of the second treatment.

1.1. Research question

Which treatment–methotrexate or mycophenolate mofetil–is more effective as a first-line immunosuppressive treatment for patients with non-infectious intermediate, posterior and panuveitis requiring corticosteroid-sparing therapy?

1.2. Specific aims

Aim 1: Establish which immunosuppressive treatment, methotrexate or mycophenolate mofetil, results in a higher proportion of patients achieving corticosteroid-sparing control of inflammation. As a primary outcome, proportion of successful corticosteroid-sparing control of inflammation will be compared at 6 months after enrollment. We will also evaluate differences in secondary outcomes, such as visual acuity, macular thickness, time to control of inflammation, efficacy within various anatomic locations of uveitis, tolerability, quality of life, and adverse events.

Aim 2: Evaluate the clinical efficacy of switching agents after initial treatment failure. Patients who are recorded as a treatment failure on the initial randomized drug will be switched to the other treatment. These patients will be followed an additional 6 months from the date of treatment failure, following the same protocol with the same primary and secondary outcomes as in Aim 1.

2. Trial design

2.1. Design summary

Study type

- Randomized, observer-masked comparative effectiveness trial
- Block randomization by site: [redacted]
- Sample size: 216 patients, 108 patients per arm (Table 1)

Treatment arms

- Oral methotrexate
- Oral mycophenolate mofetil

Treatment timeline

- Phase I
  - Initial treatment from 0-6 months. If treatment success (i.e. achieving corticosteroid-sparing control of inflammation at 6 months), treatment extended to 12 months.
- Phase II
  - Second therapy initiated after failure to achieve corticosteroid-sparing control of inflammation in Phase I (0-6 months).

Outcomes

- **Primary outcome (Specific Aim 1):**
  - Proportion of overall treatment success at 6 months, where treatment success is defined as controlled ocular inflammation (Table 2) with 7.5 mg/day of oral prednisone and ≤ 2 drops/day of topical 1% prednisolone acetate
- **Secondary outcomes**
  - Proportion of corticosteroid-sparing treatment success at 6 months after switching treatments in patients who are a treatment failure in the first 6 months where treatment success is defined as in Aim 1 **(Specific Aim 2)**
  - Time to control of inflammation
  - Time to treatment success
  - Proportion achieving treatment success at 5 months and sustaining, for at least 28 days, to 6 months
  - Proportion achieving treatment success at 12 months in Phase I
  - Phase I treatment success (6-12 months) with complete discontinuation of corticosteroid
  - Proportion achieving treatment success at 6 months in Phase II
  - Change in best spectacle-corrected visual acuity (BSCVA)
  - Presence of macular edema
  - Change in macular thickness
  - Change in vitreous haze as assessed clinically by the Miami (formerly Davis) scale
  - Change in vitreous haze as assessed by fundus photography grading by NEI and Miami (formerly Davis) scales
  - Efficacy for intermediate, posterior and panuveitis subgroups
  - Efficacy for retinal vasculitis
  - Proportion discontinuing due to intolerability
  - Rate of adverse events
  - Proportion discontinuing due to serious adverse events
  - Quality of life (Health related and vision related)

- Dose reduction
- Efficacy of treatment in patients with Vogt-Koyanagi-Harada (VKH) disease
- Proportion of patients beginning with at least 2+ inflammation in anterior chamber cells who experience a 2-step reduction (i.e. decreasing from 2+ to 0.5+; 3+ to 1+; 4+ to 2+).
- Proportion of patients beginning with at least 2+ inflammation in vitreous haze who experience a 2-step reduction (i.e. decreasing from 2+ to 0.5+; 3+ to 1+; 4+ to 2+).
- Proportion of patients who started with at least 1+ inflammation levels in anterior chamber cells who achieve a decrease to 0 level of inflammation in anterior chamber cells.
- Proportion of patients who started with at least 1+ inflammation levels in vitreous haze who achieve a decrease to 0 level of inflammation in vitreous haze.
- Proportion of patients achieving controlled inflammation defined by 0 level of inflammation in vitreous haze and 0 level of inflammation in anterior chamber cells
- Proportion of patients requiring injections for severe inflammation during the trial
- Proportion of patients requiring injections for macular edema during the trial

2.2. Study timeline

Table 1: Timeline for study completion

Date	Planned Activity
December 2011 through September 2012	Pre-study activities: refine/finalize MOP, IRB, IND, Indian Council of Medical Research approval
September 2012 through	1st meeting of DSMC, conduct final certification of sites and study personnel, earliest project start date
August 2013* through April 2017	Enrollment and follow-up
Through November 2017	Finish 6 month follow-up (Phase I) + 1 month visit window
Through May 2018	Finish follow-up (Maximum of 12 months + 1 month visit window period)
Through November 2018	Lock database, analyze, publish, and disseminate results

* [redacted] started enrollment in August 2013. Other sites on boarded at differing times after Aug 2013.

2.3. Eligibility

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2.3.1. Anatomical location of inflammation

All patients must have met the criteria for intermediate, anterior and intermediate, posterior or panuveitis, as defined by the Standardization of Uveitis Nomenclature (SUN) Working Group, at any time since their diagnosis of uveitis.

The Standardization of Uveitis Nomenclature

Type	Primary Site of Inflammation	Includes
Anterior Uveitis	Anterior Chamber	Iritis Iridocyclitis Anterior cyclitis
Intermediate Uveitis	Vitreous	Pars planitis Posterior cyclitis Hyalitis
Posterior Uveitis	Retina or Choroid	Focal, multifocal, or Diffuse choroiditis Chorioretinitis Retinochoroiditis Retinitis Neuroretinitis
Panuveitis	Anterior Chamber Vitreous Retina or Choroid	

*Adapted from the SUN Working Group Anatomic Classification of Uveitis

According to SUN criteria:

"There was consensus that the term intermediate uveitis should be used for that subset of uveitis where the vitreous is the major site of inflammation, and that the presence of peripheral vascular sheathing and macular edema should not change the classification. The diagnostic term *pars planitis* should be used only for that subset of intermediate uveitis where there is snowbank or snowball formation occurring in the absence of an associated infection or systemic disease (that is "idiopathic"). The term *panuveitis* should be reserved for those situations in which there is no predominant site of inflammation, but inflammation is observed in the anterior chamber, vitreous, and retina and/or choroid (this is, retinitis, choroiditis, or retinal vasculitis). For the definition of panuveitis, structural complications such as macular edema or neovascularization should not be considered in classifying the anatomic location of uveitis. Inflammation in the anterior chamber and vitreous (this is, more vitritis than in an iridocyclitis and more anterior chamber inflammation than in intermediate uveitis) should be referred to as anterior and intermediate uveitis and not panuveitis." [30] If vasculitis is present in the setting of intermediate uveitis, it should be called intermediate uveitis with vasculiltis, not posterior uveitis.

2.3.2. Inclusion Criteria

All the following criteria must be met at enrollment:

- History of non-infectious intermediate, anterior and intermediate, posterior or panuveitis in at least one eye
- Active inflammation within the last 180 days, defined by the presence of **any of the following** (in at least one eye) according to SUN criteria and the NEI vitreous haze grading scale:
  ≥ 2+ anterior chamber cells and/or
  ≥ 2+ vitreous haze and/or
  active retinal or choroidal inflammation
- Active inflammation in at least one eye at enrollment, defined by **any of the following**:
  ≥ 1+ anterior chamber cells and/or
  ≥ 1+ vitreous haze and/or
  active retinal/choroidal inflammation (bullous serous retinal detachment qualifies if choroidal thickening)
- **At least one** of the following criteria must be met before or at enrollment:
  1.) Active inflammation after 4 weeks of high-dose (1mg/kg prednisone equivalent) oral corticosteroid treatment
  2.) Treatment with oral corticosteroids resulting in a reduction of inflammation, followed by an increase in inflammation (of at least 1 grade in anterior chamber cells or vitreous haze or a change of non-active to active retinal/choroidal lesions) when corticosteroid is tapered, in the 180 days prior to enrollment
  3.) Treatment with ≥10mg/day oral prednisone or equivalent over at least the past 90 days prior to enrollment
  4.) Active inflammation after long-acting corticosteroid injection 4 weeks to 180 days prior to enrollment
  5.) One of the following uveitic conditions necessitating corticosteroid-sparing immunosuppressive treatment[12]:
    - Behcet's disease with posterior segment involvement
    - Multifocal choroiditis with panuveitis
    - Serpiginous choroidopathy
    - Birdshot retinochoroidopathy
    - Diffuse retinal vasculitis
    - Severe Vogt-Koyanagi-Harada syndrome (VKH) (for example: acute VKH that has been active for at least 4 weeks, or VKH with bullous serous retinal detachments and/or choroidal detachments with other signs of ocular inflammation)
    - Sympathetic ophthalmia

  6.) If the patient does not fit any of these categories, but the physician believes corticosteroid-sparing immunosuppressive therapy is indicated, eligibility may be assessed on a case-by-case basis after discussion with the coordinating center. Please contact [redacted] or by email.
- Willingness to start corticosteroid treatment at 1mg/kg or 60mg a day of prednisone, whichever is less (starting at a lower dose is acceptable if patient has known tolerability issues)
- Willingness to limit alcohol consumption (American College of Rheumatology recommendation is 2 drinks per month or less)
- Willingness to use an acceptable method of contraception during the study period (i.e. pharmacologics, devices, barrier methods) or abstinence.

2.3.3. Exclusion criteria

Any one excludes patient:

- Any infectious cause of uveitis
- Prior immunosuppressive therapy other than corticosteroids in the past 12 months
- Prior intolerability or safety issues with methotrexate or mycophenolate mofetil
- Prior failure to control ocular or other inflammation using methotrexate or mycophenolate mofetil
- Prior biologic therapy at any time
- < 16 years of age at enrollment
- Media opacity (such as cataract and/or corneal scar) and/or extensive posterior synechiae such that examination of the posterior segment is not possible in both eyes
- Chronic hypotony (IOP < 5 mm Hg for > 3 months) in both eyes
- Periocular or intravitreal corticosteroid injection in the past 4 weeks
- Fluocinolone acetonide implant in either eye in < 3 years
- Intraocular surgery in < 30 days, or planned surgery within the next 180 days
- Best spectacle-corrected visual acuity of hand motion or worse in better eye
- Planning to conceive during the study period, pregnant or breast-feeding (blood or urine pregnancy test for all females, excluding those who are post-menopausal is mandatory within 4 weeks prior to enrollment)
- History of cancer (If a patient has a history of non-melanoma skin cancer they can still be considered for inclusion in this study, provided it is not currently active).
- Systemic autoimmune disease or ocular condition (besides uveitis) anticipated to dictate treatment course
- Abnormal CBC (≤ 2,500 white blood cells and/or ≤ 75,000 platelets and/or ≤9 hemoglobin) within 4 weeks prior to enrollment*
- Abnormal alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 2 times the upper limit of normal for the lab and/or creatinine ≥ 1.5 within 4 weeks prior to enrollment
- Evidence of active tuberculosis, HIV infection, syphilis, or hepatitis B or C (patients must have a tuberculin skin test, or interferon-gamma release assay, a chest radiograph, RPR/VDRL, FTA-ABS, or other treponemal tests, Hepatitis B surface antigen and Hepatitis C antibody tests within 90 days prior to enrollment)

Beyond the tests listed above, the remainder of the work-up is at the discretion of the investigator and should be tailored to the clinical situation. Distinguishing between infectious and non-infectious uveitis is part of standard of care and should be dictated by the patient's clinical exam, but at minimum, all patients must have testing for tuberculosis, syphilis and hepatitis within 90 days prior to enrollment. If there is any clinical suspicion of infection, other tests should be considered at the investigator's discretion (i.e. leptospirosis in India). Testing is available for this at [redacted] if indicated.

2.3.3.a. Screening for Active Tuberculosis

Given that treatment with antimetabolites is not thought to increase the risk of tuberculosis, patients with latent (but not active) tuberculosis will be eligible for this study. It is at the study doctor's discretion to determine if the patient has active or latent tuberculosis, based on the testing required. There is no specific cut off for the tuberculin skin test for inclusion in the trial. Treatment for latent TB should be handled according to the standard of care in the

country in which the patient is enrolled. For example, patients with latent TB may be treated with INH in the U.S. However, this is not standard practice in India. Particular consideration to TB as an etiology should be given to patients with serpiginous chorioretinopathy, and an evaluation by an internist should be done if needed.

2.4. Randomization and masking

Block randomization of the patients will ensure that an equal number of patients are randomized to each study arm at each site. Randomization lists will be created by the biostatistician ( ) and accessed online via REDCap database. The following people will be able to access to the list of patients who have been randomized through the REDCap database:

Emergency Contact Personnel*

*Emergency contacts will log into REDCap to consult the list of randomized patients in case of an emergency in which unmasking is necessary for patient safety and of the DCC cannot be reached.

Data Coordinating Center (DCC) Personnel

The study coordinators (listed below) will be aware of patient treatment assignment and will have a copy of the patient ID list for their site; however, they will not know future treatment assignments prior to randomizing patients. After consenting patients for enrollment and confirming all eligibility requirements have been met, study coordinators will log into REDCap and perform the randomization. Study coordinators will then give patients their assigned treatment.

The following study coordinators will have access to REDCap to perform randomizations but will not know the treatment assignments prior to randomizing patients:

[redacted]

[redacted] will act as study coordinator to [redacted] patients, as well as Coordinating Center Manager overseeing all other sites. [redacted] will have access to the randomization lists for other sites, in order to check patient treatment assignment as a quality assessment and manage distribution of medications to all sites.

All patients and study coordinators will be unmasked to treatment assignment after enrollment, as the two study drugs are different in appearance and must be administered on different weekly schedules. Study ophthalmologists performing the clinical eye exams, as well as visual acuity examiners, OCT operators, fundus photographers and fundus graders will be masked to treatment assignment to prevent bias in study outcomes. The [redacted] investigational drugs department will purchase and supply mycophenolate mofetil and methotrexate.

The [redacted] will be responsible for purchasing and distributing bottles of the medications labeled with NDC/lot number and expiration dates to [redacted], who will add dosing instructions and distribute medication to [redacted] where they will distribute the medication.

Dose reduction instructions and study ID labels will be provided to each site on separate label sheets. Each site will place the study ID label on the bottle after randomization, before dispensing the drug to the patient. The format of the study ID numbers are as follows: the first character will be a number: [redacted] The next character is a checksum character, which will be a single letter. The last three characters will be sequential digits beginning at 001. An example identifier is 4J101; all identifiers have exactly five characters, and no other study at the sites uses this format.

After enrollment and randomization, the patient ID labels will be placed on the medication bottles by the study coordinator or pharmacist, depending on site-specific requirements. If a dose reduction is used, the study coordinator will place the reduction labels on the medication bottles. At no time will the study doctor handle labeling or distribution of the study medication. Study coordinators will record the study ID, drug, date dispensed, bottle number, lot number, and expiration date of each bottle dispensed during the trial in the drug accountability log.

To maintain masking throughout the trial, steps will be taken to avoid the study doctors discovering patient assignment. Not only will the study doctors have no part in handling the medication bottles, all patients will be given dark bags to place and keep their bottles in throughout the trial. They will be instructed to bring their medication to their visits enclosed in the bags, and an extra bag will be kept at the front desk of the clinics in case they forget. This will minimize the chances of the study doctor seeing the medications. Additionally, patients will meet with the study coordinator first, before seeing their study doctor. The study coordinator will review the patients' medication calendars with them and keep the calendars and study bottles in his/her office for the entire patient visit. Before bringing patients to the study doctor, the study coordinator will remind them to not discuss their dosing and

medication name with their study doctor.

Clinical examiners, refractionists, OCT operators, fundus photographers and fundus graders will not be given any information on medication assignment. If personnel are unmasked at any time, a protocol deviation form must be completed, scanned and emailed to both the Medical Monitor ([redacted]), Principal Investigator ([redacted]) and Coordinating Center Manager ([redacted]). Note that these patients should still continue in the trial.

2.5. Definitions for primary endpoint

2.5.1. Determination of Treatment Success/Failure

Treatment success is defined as controlled ocular inflammation (see Table 2) in both eyes with 7.5 mg/day of prednisone, no periocular or intravitreal corticosteroid injections after the first 90 days of follow up, and ≤ 2 drops/day of topical 1% prednisolone acetate at the 6 month visit without treatment failure any point due to safety, tolerability or futility. Patients can stop medication at any time, but that in and of itself does not count as a treatment failure.

Table 2: Criteria for *controlled* inflammation

Parameter	Definition of control
Anterior chamber cells*	≤ 0.5+
Vitreous haze**	≤ 0.5+
Choroid & retina***	No active inflammation or retinal vasculitis posterior to the equator

*SUN criteria[30]; ** NEI vitreous haze grading scale[31] *** Cystoid macular edema is not sufficient to be called active inflammation

2.5.2. Treatment failure

- **Failure due to *efficacy*:** Patients can be declared a treatment failure due to futility and be declared a treatment failure and enter Phase II **at any time during follow-up** if the following occurs: The treating physician determines that it is futile to continue the current study medication due to persistent, uncontrolled inflammation that appears to be non-responsive to treatment. This option of declaring futility should only be declared if treatment with study medication seems completely unlikely to be able to control inflammation. Since the medications take up to a few months to fully take effect, increase in inflammation early on in the trial is not an indication of treatment failure. Corticosteroids may be increased in the case of increased inflammation.

  Efficacy will be judged at the primary endpoint of 6 months. Specifically, at 6 months, if there is a lack of efficacy, patients will be declared a treatment failure and enter Phase II if the following occurs: The patient does not have controlled inflammation (see Table 2) with a prednisone dose of 7.5 mg/day and less than or equal to 2 prednisolone acetate 1% drops per day by 6 months.

- **Failure due to *intolerability*:** Patients who experience severe symptoms thought to be related to the drug should try a dose reduction if they are willing. If this is not successful and the patient is unable to continue their

medication due to symptoms and is also not willing to continue, treatment failure can be declared. Please refer to Table 5 for dose reduction guidelines. Trial of a dose reduction is strongly encouraged, however it **is not required** for a patient to be determined a treatment failure due to intolerability.

- **Failure due to *safety*:** Patients who experience abnormal lab results meeting the designated threshold of a *non-serious adverse event* (e.g. AST or ALT increasing to twice the upper limit of normal) will immediately stop taking their medication. As these abnormalities are often reversible, patients whose abnormalities are classified as non-serious adverse events (see Table 3) will be *allowed 28 days to regain eligibility*. It is recommended that these patients repeat lab tests within 1-2 weeks of the initial abnormal result to see if the results return below the designated threshold (e.g. AST or ALT less than twice the upper limit of normal). If the lab results return below the designated threshold of a *non-serious adverse event* within 28 days, patients may be re-administered the study drug per protocol or at one of the designated dose reduction levels, at the investigator's discretion.

  If lab results remain at or above the threshold of a *non-serious adverse event* for 28 days, this is classified as a serious adverse event and treatment failure will immediately be declared. At this point, patients will be treated according to the best medical judgment of their clinician and not switch to Phase II (if currently in Phase I). However, month 6 visit data and imaging should still be collected (Phase I and Phase II), if the serious adverse event occurs before the six month visit. For other non-serious adverse events (such as an opportunistic infection) the study drug may be stopped temporarily as per the discretion of the investigator. If an infection does not resolve within 28 days, it is considered a serious adverse event.

Table 3: Thresholds for classifying non-serious and serious lab abnormalities

	Non-Serious Adverse Event*	Serious Adverse Event
Leukocytes	>1,000 to <2,500/µL	≤ 1,000/µL
Platelets	20,000 to 75,000/µL	< 20,000/µL
Hemoglobin	≥ 6.5 to < 9 g/dL	< 6.5 g/dL
SGOT (AST) or SGPT (ALT)	2 to <5 times the upper limit of normal of the reference range	≥ 5 times the upper limit of normal of the reference range
Creatinine	≥ 1.5 to < 2 mg/dL	≥ 2 mg/dL

*NOTE: If any non-serious lab abnormality does not resolve within 28 days, then it must be classified as a serious adverse event, and treatment failure due to safety will be declared.

For all non-laboratory SAEs, treatment failure cannot be declared until the Medical Monitor judges that the SAE is related to the study drug. This will require the investigator notifying the Medical Monitor about the event, and the Medical Monitor contacting the investigator regarding his determination. The Medical Monitor will determine two things: 1, whether this is a true treatment failure because the SAE is likely to be related to the study drug, and 2, whether it is safe to switch the patient to Phase II. If it is not safe to switch, the patient will be treated according to best medical judgment, and still be followed up at their 6 month visit (Phase I and Phase II).

If the investigator thinks the SAE is related to the study drug, he/she can stop the study medication anytime (including prior to determination of treatment failure by the Medical Monitor). If the investigator thinks treatment failure is likely (prior to hearing from the Medical Monitor) they should obtain all study assessments which would be collected at a treatment failure visit. However, the investigator will wait to complete the Treatment Assessment Form and officially declare treatment failure until they are instructed to do so by the Medical Monitor.

2.5.3. Dropouts, Non-Compliant Patients and Follow-up

- **Dropout from study:** Patients will be considered to have dropped out from the study only if they **declare they are no longer interested in further participation and not willing to return for any study visits, or are deceased**. If patients are not willing to return for any study visits, no further information will be collected on those patients. We anticipate that a few patients may drop out due to unwillingness to continue or death. In case of patient dropout, the patient dropout form should be filled out.

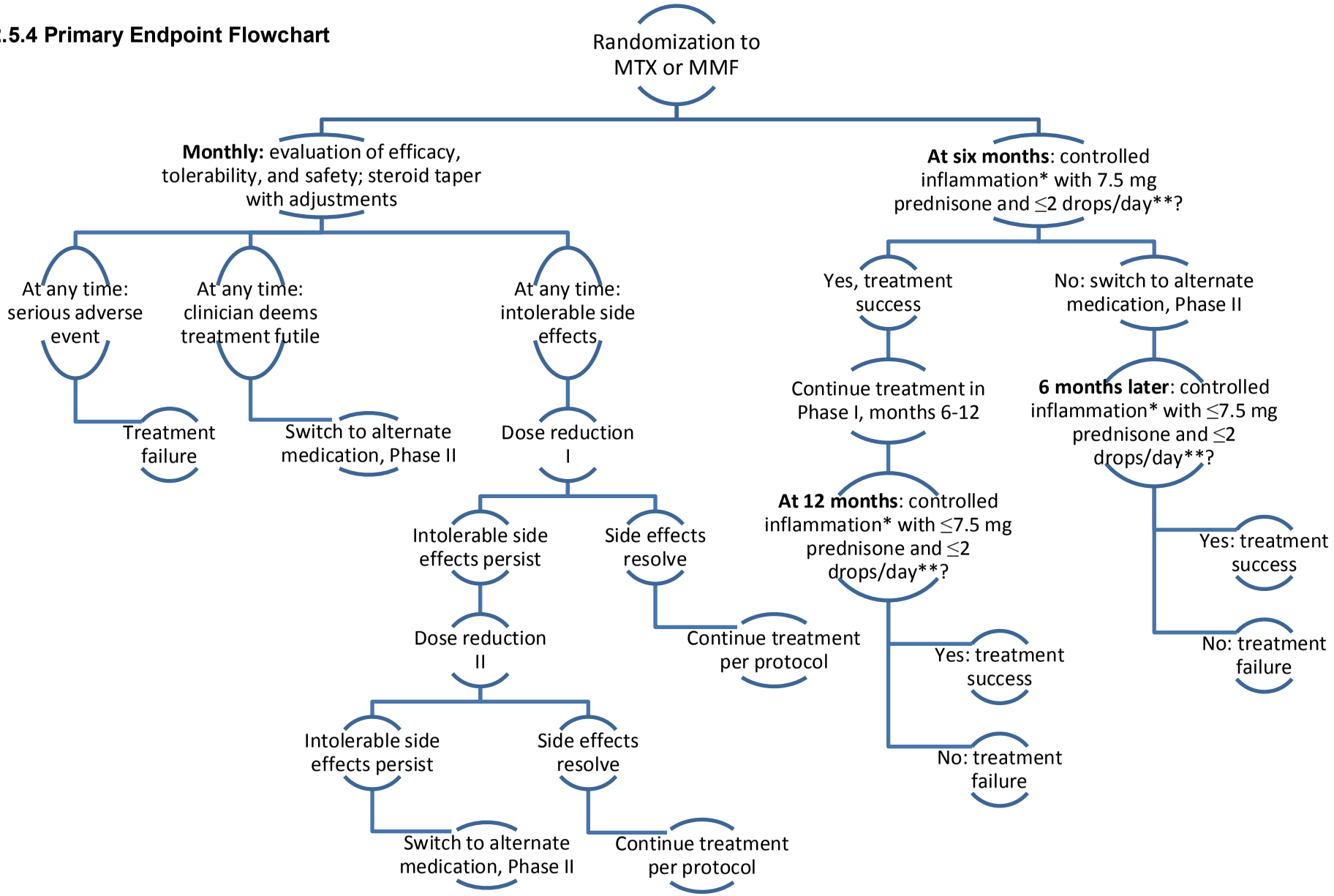
  If death is considered to be related to the study drug, the patient will be counted as a treatment failure. If death is not related to the study drug, the patient will be counted as a dropout. This would be at the discretion of the Medical Monitor.

- **Non-compliant Patients:** Patients who stop the study treatment for reasons other than efficacy, tolerability and/or safety (i.e. fear of potential side effects) but are willing to return for study visits, are not considered dropouts. Also, if patients miss study visits, and do not respond to contact, they are not considered dropouts. These patients will be considered **non-compliant patients,** and will be encouraged to return for subsequent study visits regardless of whether or not they are taking study medication, especially the 6 month visit (Phase I and Phase II).

  It should be noted that missing a visit does not mean that a patient has dropped out of the study. These patients are considered to be non-compliant. For example, if they missed the 1 month visit, every attempt will be made to bring them back as soon as possible and to continue with subsequent visits. Also, a non-serious adverse event or discontinuation of study medication does not mean that the patient has dropped out and they should continue to be followed according to the protocol, as they may be able to resume treatment. Even if the patient is not willing to resume treatment, but is willing to return for study visits they are not considered dropouts.

- **Following Patients who fail prior to Phase I & Phase II (6 months)**: If patients are declared a treatment failure prior to Phase I or Phase II 6 Months, every effort should be made to bring the patient back for the 6 month visit. Note, that patients who are declared treatment failure, and are switching from Phase I to Phase II will already be followed.

2.5.4 Primary Endpoint Flowchart



*Criteria for controlled inflammation: Anterior chamber cells ≤0.5 +; Vitreous haze ≤ 0.5 +; No active choroid and retina lesions
** 2 drops/day refers to topical 1% prednisolone acetate or equivalent

3. Treatment plan

3.1. Study drugs

Patients will be randomized to receive either methotrexate or mycophenolate mofetil. In addition, folic acid supplements will be given to all patients who have been randomized to methotrexate. **All study ophthalmologists, refractionists, OCT operators, fundus photographers and fundus graders will be masked to treatment assignment.** For dosing schedules, see Tables 4 and 5.

To maintain masking, study coordinators will review patient side effects with the patient at each visit, prior to meeting with the physician. At this time, the study coordinator will remind the patient **not to speak to their study doctor regarding the name of the medication or dosing instructions**. If the patient is experiencing intolerable side effects, the study coordinator and patient will speak with the study doctor about the possibility of a dose reduction, without revealing the name of the medication or the dosing instructions. The study doctor will then decide if the dose reduction should be tried and communicate this with the patient and study coordinator. The study coordinator will then provide the patient with new dosing instructions, away from the vicinity of the study physician (see Table 5).

Table 4: Weekly Dosing Schedule

	Drug	Day 1	2	3	4	5	6	7
Introductory Dose	Methotrexate	7.5 mg BID						
Weeks 1&2	Mycophenolate Mofetil	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID
	Folic Acid (*methotrexate only*)	1 mg daily	1 mg daily	1 mg daily	1 mg daily	1 mg daily	1 mg daily	1 mg daily
Maintenance Dose	Methotrexate	12.5 mg BID						
Post week 2	Mycophenolate Mofetil	1.5 g BID	1.5 g BID	1.5 g BID	1.5 g BID	1.5 g BID	1.5 g BID	1.5 g BID
	Folic Acid (*methotrexate only*)	1 mg daily	1 mg daily	1 mg daily	1 mg daily	1 mg daily	1 mg daily	1 mg daily

Table 5: Dose Reduction Guidelines*

	Drug	Day 1	2	3	4	5	6	7
Reduction Level I	Methotrexate	10mg BID						
	Mycophenolate mofetil	1g BID	1g BID	1g BID	1g BID	1g BID	1g BID	1g BID
Reduction Level II	Methotrexate	7.5mg BID						
	Mycophenolate mofetil	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID	500 mg BID

*Doses should only be reduced in response to intolerable side effects and safety concerns. If there are no tolerability/safety issues, the patient should stay on the maintenance dose for the duration of follow-up. Note: Even if a dose reduction is used for methotrexate, folic acid should remain at 1 mg daily.

All individuals handling methotrexate and mycophenolate, including study participants and/or family members/others caring for and assisting study participants with their medications outside of the hospital/clinic, will be educated on the Safe Handling of Hazardous Medications guidelines outlined in the National Institute for Occupational Safety and Health manual, Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings.

The National Institute for Occupational Safety and Health manual can be found at:
http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf

3.1.1. Methotrexate

All methotrexate doses **will be taken once per week in a divided dose**, one dose taken in the morning and one in the evening. Patients on methotrexate will be instructed to take their medication with food. For the first two weeks, an introductory dose of 15 mg/week (7.5mg BID once a week) orally will be administered to assess tolerability. This means taking 3 pills in the morning and 3 pills in the evening once a week. Patients should be instructed at the Enrollment/Baseline visit to begin methotrexate on a day that is convenient for them, within 6 days of enrollment. After two weeks, the dose will be increased to 25 mg/week (12.5mg BID) This means taking 5 pills in the morning and 5 pills in the evening once a week, until the end of follow-up or until treatment failure due to intolerability, adverse events, or of lack of efficacy.

If there are tolerability issues in the first two weeks such that the patient is not able to increase the dose, and unwilling to continue the current dose, treatment failure due to intolerability should be declared. The patient would then be eligible to switch treatment in Phase II. If this occurs in Phase II, treatment failure would be declared and patient will be treated according to best medical judgment. If the dose is increased per protocol at two weeks, the study ophthalmologist can decide to reduce the maintenance dose if the patient experiences severe side effects.

3.1.1.a. Dose Reduction MTX

If the patient is experiencing intolerable side effects, the study coordinator and patient will speak to the doctor about the possibility of a dose reduction, without revealing the name of the medication or the dosing instructions. The study doctor will then decide if the dose reduction should be done and inform the study coordinator and patient. The study coordinator will then provide the patient with new dosing instructions, away from sight of study physician. A dose reduction is not mandatory but is encouraged in the setting of intolerability.

For the first dose reduction, methotrexate will be reduced to 20 mg/week (10mg BID, once a week). This means taking 4 pills in the morning and 4 pills in the evening once a week. If side effects persist and the study ophthalmologist wishes to reduce the dose a second time, the dose will be reduced to 15mg/week (7.5mg BID, once a week). This means taking 3 pills in the morning and 3 pills in the evening, once a week. After the second dose reduction, treatment can be stopped if intolerability persists and the patient can switch to Phase II.

Although dose reductions are strongly encouraged, they **are not mandatory to attempt before determining treatment failure**. Treatment failure due to intolerability can be declared without trial of a dose reduction.

If a dose reduction has been utilized, and the investigator feels that the tolerability/safety issues have been resolved, it is at their discretion to return the patient to the maintenance dose level of the medication.

3.1.2. Mycophenolate Mofetil

Mycophenolate mofetil **will be taken twice daily**. Patients on mycophenolate mofetil will be instructed to take their medication on an empty stomach with no food one hour before or after taking each dose. For the first two weeks, an introductory dose of 500 mg BID orally will be administered to assess tolerability. This means taking one pill in the morning and one pill in the evening. After two weeks, the dose will be increased to 1.5 g BID. This means taking 3 pills in the morning and 3 pills in the evening until the end of follow-up or until treatment failure due to intolerability, adverse events, or lack of efficacy.

If there are tolerability issues in the first two weeks such that the patient is not able to increase the dose, and also is unwilling to continue, treatment failure due to intolerability should be declared. The patient would then be eligible to switch treatment in Phase II. If this occurs in Phase II, treatment failure would be declared. If the dose is increased per protocol at two weeks, the study ophthalmologist can decide to reduce the maintenance dose if the patient experiences severe side effects.

At any point if treatment failure is declared due to tolerability, the patient should be treated according to best medical judgment and still be followed up to their 6th month assessment (Phase I and Phase II).

3.1.2.a. Dose Reduction Mycophenolate Mofetil

If the patient is experiencing intolerable side effects, the study coordinator and patient will speak to the doctor about the possibility of a dose reduction, without revealing the name of the medication or the dosing instructions. The study doctor will then decide if the dose reduction should be done and inform the study coordinator and patient. The study coordinator will then provide the patient with new dosing instructions, away from sight of study physician. A dose reduction is not mandatory but is encouraged in the setting of intolerability.

For the first dose reduction, mycophenolate will be reduced to 1g BID. This means taking 2 pills in the morning and 2 pills in the evening. If side effects persist and the study ophthalmologist wishes to reduce the dose a second time, the dose will be reduced to 500 mg BID. This means taking 1 pill in the morning and 1 pill in the evening. After the second dose reduction, treatment can be stopped if intolerability persists and the patient can switch to Phase II.

Although dose reductions are strongly encouraged, they **are not mandatory to attempt before determining treatment failure**. Treatment failure due to intolerability can be declared without trial of a dose reduction.

If a dose reduction has been utilized, and the investigator feels that the tolerability/safety issues have been resolved, it is at their discretion to return the patient to the maintenance dose level of the medication.

3.1.2.b. Proton Pump Inhibitors and Mycophenolate Mofetil

Upon entering the trial some patients may be taking proton pump inhibitors (e.g. omeprazole). Due to a potential interaction with mycophenolate mofetil, H2 blockers are preferred over proton pump inhibitors. However, proton pump inhibitors are acceptable if the physician and/or patient does not want to change. This should be noted on the Baseline History Form under current systemic medications.

3.1.3. Folic acid

It is standard of care to prescribe folic acid supplements to reduce the severity of side effects in patients treated with methotrexate. All patients randomized to methotrexate will be prescribed 1mg per day of folic acid. It is fine to take folic acid the day methotrexate is taken.

3.1.4. Packaging and distribution of study medications

Patient medications will be purchased and packaged by [redacted], printed with the medication name, lot number, and expiration date. [redacted] will be responsible for distributing medications and labels with dosage instructions to all other sites.

Initial dose bottles will contain 14 days of medication at the lower initial dose. The initial two-week supply of methotrexate is 12 pills, and the initial two-week supply for mycophenolate mofetil is 28 pills. Maintenance dose bottles will contain 30 days' worth of medication, plus additional pills as a buffer for visit scheduling. Methotrexate maintenance dose bottles will contain 50 pills each. Mycophenolate mofetil maintenance doses will be provided in bottles of 100 pills each.

At the patient's first visit (i.e. Baseline for Phase I) they will be given the 14 day introductory dose and either one maintenance dose bottle of mycophenolate (100 pills) or one maintenance dose bottle of methotrexate (50 pills). At every monthly visit following, patients will be given an additional 30 days' worth of medication (50 pills of methotrexate, or 200 pills of mycophenolate) until 5 months. If a patient needs to schedule their appointment beyond the visit window allowed by the medication supply, additional bottles may be dispensed to ensure sufficient supply of medicine, although this scheduling should be discouraged.

If patients enter Phase II after treatment failure in Phase I, patients' medication will be dispensed following the same schedule as in Phase I. If patients enter Phase I (6-12 months) after treatment success in Phase I (0-6 months), they will be given 120 days' worth of medication at their 6 month visit. Lost bottles will be replaced.

Study medications, labeled with the appropriate dosing instructions, will be distributed to the study coordinator prior to each study visit. After randomization, before the drug is dispensed, the study coordinator will place the Study ID label on the bottles. If a dose reduction is used, the study coordinator will put a label on the bottle with the new instructions.

Study coordinators will also place number labels, provided by the coordinating center, on all bottles in order to track which individual bottles were dispensed to patients. Study coordinators will indicate on the Medication Log, what type of bottle they have dispensed (i.e. initial or maintenance), how many bottles, what type of bottle has been returned, and the numbers of the bottles.

If at any time the patient fails to bring in their used maintenance bottles, the study coordinator should refer to the clinic staff member responsible for maintaining the randomization list to verify patient assignment. This will ensure that the patient is given the correct maintenance bottle corresponding to their assignment.

3.1.5. Adherence to the treatment plan

Patients will be given a treatment diary in the form of a monthly calendar on which they will be asked to record the medications they are taking as well as reasons for missed doses. They will be asked to bring the calendars with them to each visit. Adherence will be monitored by the study coordinator through review of the calendars, and will be recorded on the Medication Log in each patient file. Pill counting of pills in bottles remaining from the previous study period will also be done for a more objective measure of adherence. If a patient has just started on a new bottle shortly before the visit, do not count these pills. For instance, if a patient returns for their two week visit two weeks plus two days after the baseline visit, the study coordinator will not count the pills remaining in the maintenance dose bottle they have just started on. If the patient fails to bring in their calendar, the study coordinator should ask the patient to estimate the number of doses they have missed.

3.1.5.a. Missed Doses

The following instructions will be given to the patients if they miss scheduled doses of their medication:

Methotrexate: If a patient misses their scheduled dose, they may take it the next day. If it is not taken the next day, they should wait until the following week. If patients make-up their dose on the next day, they should continue their medication weekly from the original day.

Mycophenolate Mofetil: If the patient misses a dose, they should continue with the regular dosing schedule.

3.2. Corticosteroid therapy

3.2.1. Oral prednisone

Prednisone vs. alternative oral corticosteroid

Unless contraindicated, oral prednisone should be used. An equivalent dose of an alternative oral corticosteroid may be used only if a specific contraindication to oral prednisone is present. All references to oral corticosteroid and specific dosing schedules presented in this Manual of Procedures are given for oral prednisone.

Initial dose

All patients enrolled in the study will be initially taking concomitant oral corticosteroids at 1 mg/kg or 60 mg daily, whichever is less. Treatment success is dependent upon successfully tapering concomitant prednisone to 7.5 mg/day. Initial corticosteroid dose will be continued for 2 to 4 weeks at which point prednisone will be gradually tapered.[1] Prednisone will be tapered to and held at 7.5 mg/day for the first 6 months of the study. Further reduction of corticosteroids will be allowed in Phase I after six months. If patients switch treatments and enter Phase II due to a failure of efficacy in Phase I, they will follow the same protocol as the initial Phase I corticosteroid

treatment and begin at 1 mg/kg or 60 mg, whichever is less. In patients failing for efficacy, investigators may start at a lower prednisone dose if they feel it is medically indicated. However, following the corticosteroid tapering guidelines is strongly encouraged. If patients switch treatments and enter Phase II due to a failure of intolerability in Phase I, then it is at the study doctor's discretion at what dose of corticosteroid to start the patient.

Tapering schedule

For all patients, oral prednisone will be tapered gradually according to Standardization of Uveitis Nomenclature (SUN) guidelines (see Table 6). As it takes 6-8 weeks for the study medications to take full effect, it is expected that inflammation may become uncontrolled with a corticosteroid taper in some patients during the first 3 months of the study. This does not necessarily mean that the randomized treatment has failed, since more time may be needed to ensure the drug has reached its full effect. If the study ophthalmologist believes that continued treatment is futile prior to the primary endpoint, treatment failure may be declared and the patient should enter Phase II. If this occurs in Phase II, treatment failure will be declared and the patient should be treated according to best medical judgment. However, all patients should be followed up to their 6th month assessment in Phase II.

At any point in Phase I or Phase II, investigators have the option of reducing the prednisone dose, and following a faster taper, if the patient is experiencing severe side effects. However, it is strongly encouraged that investigators follow the corticosteroid tapering guidelines. If **absolutely medically necessary**, the investigator may digress from the protocol and reduce steroids below 7.5 mg/day in the first six months, but this is strongly discouraged.

The corticosteroid tapering schedule for Phase I (6-12 months) is optional, and physicians may taper patients as they deem medically acceptable. It is not mandatory for patients to reduce down to 0mg of prednisone by 12 months. In general, a rapid taper in Phase I months 6-12 is not recommended due to issues of adrenal insufficiency.

Table 6: Tapering schedule for oral prednisone: Phase I or if starting new medication in Phase II*

Dose (mg/day)	Duration (weeks)	Decrement (mg/day)
60	2 – 4[1]	10
50	1	10
40	1	5
35	1	5
30	1	5
25	1	5
20	1	2.5
17.5	1	2.5
15	1	2.5
12.5	1	2.5
10	1	2.5
7.5	hold*	

NOTE: Begin patients at 1mg/kg or 60 mg/day, whichever is less. For Phase I hold patients at 7.5 mg/day, up to the end of 6 months.
*If starting Phase II and failed Phase I due to efficacy.

[1] If uveitis does not improve at the end of the first 4 weeks, use best medical judgment regarding supplemental treatment (e.g. pulse dose treatment, corticosteroid injections, additional immunosuppressives).

Table 7: Optional tapering schedule Phase I (6-12 months)

Dose (mg/day)	Duration (weeks)	Decrement (mg/day)
7.5	1*	2.5
< 7.5 & ≥ 5	2 – 4	1 - 2.5
< 5 & ≥ 2.5	2 - 4	1.5 - 2.5
< 2.5 & ≥ 1	2 – 4	1
0		

NOTE: When beginning Phase I (6-12 months), hold patient at 7.5 mg/day, for at least one week.

Directions for Rescue Taper

Reactivations can be mild or severe. Mild reactivations are considered an increase in inflammation up to the 1+ level in anterior chamber cell or vitreous haze. Severe reactivations are considered an increase in inflammation up to the 2+ level or higher in anterior chamber cell or vitreous haze. Retinal/choroidal lesions may be considered mild or severe at the discretion of the study physician.

If uveitis reactivates:

- Increase oral prednisone up to a dose of 1 mg/kg for severe reactivations, or for mild reactivations, up to double the dose at which the flare occurred, until uveitis is controlled. Then re-taper according to the guidelines.

Uveitis is considered non-responsive if inflammation does not increase but does not further improve after the first 4 weeks of treatment on 1mg/kg oral prednisone.

If uveitis is non-responsive:

- Hold the current dose of prednisone for an additional week. If still no improvement, treatment failure due to futility may be declared, and patients may proceed to Phase II. Alternatively, other therapies may be added, but these should be noted as a protocol deviation.
- If treatment failure is declared due to futility in Phase I, before the primary endpoint of 6 months, patients may switch to Phase II. Patients who refuse to switch to Phase II should be encouraged to return for a 6-month visit. Patients who switch to Phase II will already be followed.
- If treatment failure is declared due to futility in Phase II, before the primary endpoint of 6 months, patients will be treated according to best medical judgment. If treatment failure is declared prior to 6 months, Phase I and Phase II, every attempt must be made to bring patients back for their 6 month assessment.

After suppression of uveitis is once again achieved (either in the case of reactivation or non-response) follow the taper guidelines for Phase I. Patients who have failed the treatment to which they are randomized will then switch treatments, begin Phase II, and follow the same taper guidelines as Phase I (0-6 months). If patients flare during Phase II, they can follow directions for the rescue taper listed above. Patients who fail the second treatment at the 6 month endpoint will be treated as per the investigators discretion.

3.2.2. Supplements

All patients will be given recommendations for supplemental treatment. This treatment is important for patients receiving oral corticosteroids, in order to minimize the incidence of osteoporosis. Recommendations will include:

- Calcium supplement, 500 mg 3 times daily (unless contraindicated)
- Vitamin D, 400-800 IU daily.

3.2.3. Topical corticosteroid

In addition to oral prednisone, patients may enter the study on varying doses of topical corticosteroid drops. Topical corticosteroids should be tapered according to the suggested guidelines (Table 8). Various types of topical corticosteroids are acceptable. The chronic use of two times a day prednisolone acetate 1% was considered to be medically acceptable in a survey we conducted of the American Uveitis Society members. Thus, a dose of ≤ 2 drops a day prednisolone acetate 1% or equivalent corticosteroid will be considered sufficient in order to declare treatment success. If possible, the goal will be to completely taper off topical corticosteroids. In order to determine treatment success or failure, the equivalent amount of prednisolone acetate 1% would have to be determined, and if greater than 2 times a day treatment failure will be declared.

Table 8: Suggested tapering schedule for topical corticosteroid drops

Dose	Duration (weeks)
1 drop, 8-10 times a day	1-2
1 drop, 6 times a day	1
1 drop, 4 times a day	1
1 drop, 3 times a day	1
1 drop, 2 times a day	1
1 drop, 1 time a day	1
None	

3.2.4. Periocular and Intravitreal Injections

The use of periocular and intravitreal injections during the trial is strongly discouraged, as it hinders the ability to assess the study drugs' effectiveness for controlling inflammation. One injection, either periocular triamcinolone 40mg or intravitreal triamcinolone 4mg, may be administered to treat persistent macular edema during the first 90 days of follow-up if the investigator thinks this is medically necessary. One injection for persistent macular edema is permitted in the first 90 days of follow-up of Phase I, and similarly, one injection treating persistent macular edema is permitted in the first 90 days of follow-up of Phase II. If an injection is given at any time solely for the purpose of treating inflammation, a Protocol Deviation Form should be completed and sent to the Medical Monitor ([redacted]), Principal Investigator ([redacted]), and Coordinating Center Manager ([redacted]). If an injection is given for any reason after the first 90 days of follow-up of either Phase I or Phase II, a Protocol Deviation Form should be completed and sent to the Medical Monitor, Principal Investigator, and

Coordinating Center Manager.

3.2.5 Other adjunctive treatments/procedures

The protocol dictates use of oral prednisone, corticosteroid drops and study medication (methotrexate or mycophenolate). The investigator may use other topical adjunctive medications such as IOP lowering medications and cycloplegic agents. These should be recorded on the Treatment Assessment form at each visit. The protocol does not allow for intravenous therapy, additional immunosuppressives or surgery during the study period. If such therapies are deemed necessary, the Protocol Deviation form should be completed and sent to the Medical Monitor, Principal Investigator, and Coordinating Center Manager.

3.3. Study procedures

Enrollment/Baseline visit

Study coordinators should adhere to the following protocol for study procedures taking place at the enrollment visit.

- The patient's eligibility for participating in the study will be determined by the study ophthalmologist, aided by the study coordinator.
- If eligible, the patient will review the consent form with the study coordinator and the study physician, and give their consent.
- After consent, the study coordinator will assign the patient a unique Patient ID (derived from the list provided to study coordinator by the principal statistician).
- The study coordinator will then contact the designated person on site, holding the randomization list, to obtain the patient's drug assignment. This will be done away from sight of the study physician.
- The study coordinator will then label the medication with the assigned Patient ID. They should also place the appropriate number for the bottles (i.e. if it is the first bottle dispensed, it should have the #1 on the bottle).

Study visits

Study coordinators should adhere to the following protocol for study procedures taking place, after the patient is consented, enrolled and randomized. All study procedures should follow the schedule listed below:

- The patient comes for a study visit and meets with the study coordinator before their study doctor.
- The patient's medication bottle and folic acid bottle (*if applicable*) is immediately placed in a secure, opaque bag and left at the study coordinators desk for the remainder of the visit. Patient medication calendars should also be placed in the opaque bag.
- The study coordinator will check-in with the patient and complete the following in any order:
    - Review of patient medication diaries
    - Review of adverse events since last visit*
    - Dispense new medication bottle (*if applicable*)
    - Completion of SF-36 questionnaire (All patients) (*if applicable*)

- Completion of NEI-VFQ-25 (all patients) and IND-VFQ (Indian patients only)
- Remind the patient that they should not speak to their study doctor about their dosing schedule, or the name of the medication that they are currently taking.

*If the patient is experiencing intolerable side effects, the study coordinator and patient will speak to the doctor about the possibility of a dose reduction, without revealing the name of the medication or the dosing instructions. The study doctor will then decide if the dose reduction should be done and inform the study coordinator and patient. The study coordinator will then provide the patient with new dosing instructions, away from sight of study physician. A dose reduction is not mandatory but is encouraged in the setting of intolerability.

- The patient will then complete the study assessments, in the following order:
  - Visual Acuity Assessment
  - Slit lamp front of the eye exam and intra-ocular pressure
- The patient's eyes will then be dilated and the following assessments will be completed, in any order**:
  - Posterior segment exam
  - OCT imaging
  - Fundus photography
  - Fluorescein angiogram (not a study assessment, but if performed results should be recorded)
  - Laboratory measurements
- After completion of the study visit, the patient will meet with the coordinator, review scheduling for the next study visit, and retrieve their medication.

**It is essential that visual acuity measurements, front of the eye exams and intra-ocular pressure are completed *before* dilation of the eyes.

Data handling and data entry
After completion of each study visit, study coordinators at all sites will scan data collection forms and send them electronically in PDF format to the study email address ([redacted]). Hard copies of the forms should be kept in a secure location at each site. Study staff at [redacted] will perform double data entry of the PDF forms into a web-based REDCap database from which data can be electronically extracted for analysis. See section 7 for further details on the data entry process.

4. Study visits

4.1. Visit schedules

4.1.1. Phase I: First-line treatment

After eligibility has been evaluated and informed consent given for participation in the trial, patients will be randomized to receive oral methotrexate or mycophenolate mofetil. Patients will continue with this course of treatment unless treatment failure occurs due to safety, intolerability or lack of efficacy. If a failure is recorded within the first 6 months, the treatment assignment will be switched to the drug not initially randomized to, and the patient will follow a new visit schedule.

Patients who are treatment failures in Phase I due to safety (i.e. a serious adverse event deemed to be related to the study drug by the Medical Monitor) may or may not proceed to

Phase II depending on the Medical Monitor's determination. In most cases of an SAE, the patient will likely not be allowed to switch to Phase II, but in some cases, such as an SAE due to intolerability, it may be deemed safe to switch to Phase II. Even if the patient does not switch to Phase II, outcome data at 6 months should be collected if the patient is willing.
Treatment success, according to the primary endpoint, will be assessed at 6 months. If treatment has been deemed successful for a patient at 6 months, they will be provided study medication for an additional 6 months and return for additional study visits as shown below. As long as the patient stays on the first randomized medication, Visit Schedule I will be followed.

Guidelines for Visit Schedule I

- Day 1 corresponds to the Baseline-I visit, which is also the first day the patient receives treatment.
- Visit windows are determined based on the date of randomization.
- The baseline eye exam and other baseline assessments may be collected at a separate visit up to 14 days before the patient is enrolled and randomized. Laboratory measurements may be collected within either 4 weeks or 90 days prior to the date of randomization, depending on the laboratory test.
- There should be a minimum of 2 weeks between each study visit.
- Data for the baseline and follow-up visits may be collected anytime within the visit window.

Table 9: Visit Schedule Phase I (0-6 months) or Phase II

Visit	Window Days/Weeks
Baseline*	
Week 2	±3 days
Month 1*	±15 days
Month 2	±15 days
Month 3	±15 days
Month 4	±15 days
Month 5	±15 days
Month 6	-15 to +30

*Every monthly visit scheduled will be calculated from the baseline visit date (Phase 1), using the average amount of days per month. If a patient does not come in within the visit window, every attempt should be made to get them in for a clinic visit as soon as possible.

Table 10: Visit Schedule Phase I (6-12 months)

Visit	Window (Weeks)
Month 9*	±15 days
Month 12*	-15 to +30

* Since baseline/treatment administration (Phase 1)

4.1.2. Phase II: Rescue treatment

In case of the first randomized treatment failure due to intolerability or lack of efficacy within the first six months of treatment, the treatment assignment will be switched to the alternate treatment. At this point, the patient will receive the antimetabolite not originally randomized to and will be followed an additional 6 months or until failure of the second treatment.

Patients will be given 2 weeks to enter into Phase II after treatment failure in Phase I. If patients do not enter within the 2-week window, they should be treated according to best medical judgment of their physician. If the physician believes a patient would benefit from treatment in Phase II, but there is an exceptional circumstance preventing the patient from entering Phase II within the 2-week window, contact the Coordinating Center for assistance.

Guidelines for Visit Schedule II

- Day 1 corresponds to the Baseline-II visit, which is also the first day the patient receives rescue treatment with the medication not initially received. Day 1 may be its own visit date (i.e. if within 2 weeks of the end of Phase I). Alternatively Day 1 may be the same day as the last day of Phase I. All study forms should indicate what visit it is for Phase I and what visit it is for Phase II, if applicable. See the following example below.

Phase	☒ 1 ☒ 2
Visit	☒ Baseline ☐ Two weeks ☐ Non-study visit (treatment failure only)
	Month: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☒ 6 ☐ 9 ☐ 12

- Visit dates are determined based on the date of the Baseline-II visit (which may be the same date as Phase I treatment failure), and may not be changed.
- The Baseline-II visit form should be completed to gather information on any changes in health status or medications.
- There should be a minimum of 2 weeks between each study visit.
- Data for the follow-up visits may be collected anytime within the visit window.

4.1.3. Non-study visits

Despite the regular follow-up outlined in the visit schedules above, it is anticipated that some patients will have inflammation that is difficult to control or be intolerant to the drug, leading to additional visits. These additional visits may not fall within the study visit window. It is possible that the circumstances leading to such visits may result in changes to oral or topical corticosteroid dose, or a declaration of treatment failure and a need for rescue treatment. If treatment failure is declared at a non-study visit, all of the forms required at the time treatment failure is declared should be completed.

Guidelines for non-study visits

- Any changes to oral or topical corticosteroid dose will be noted on the appropriate form during the next scheduled study visit.
- If a treatment failure is declared at a non-study visit during follow-up while being treated during…
  - Phase I (initial randomized treatment): Record a treatment failure using Treatment Assessment Form. Perform Baseline II visit at this time or within 14 days. Phase II rescue treatment can start immediately.
  - Phase II: Record a treatment failure using the Treatment Assessment Form. Patient should continue to be followed until 6 months and 6th month data collected.
  - If treatment failure is declared at a non-study visit, an attempt should be made to collect as much information as possible, including the forms listed in Section 4.2.

4.2. Study form completion schedule

Forms	PHASE I					PHASE II				
	Baseline : Phase I	Week 2	Follow up months 1-5, 9	Treatment Failure anytime*	Follow up months 6 &12	Baseline: Phase II**	Week 2	Follow up months 1-5	Treatment Failure anytime*	Follow up month 6
Eligibility/ Screening Form	X									
Consent Form	X									
Baseline History Form	X									
Clinical Eye Exam Form	X		X	X	X			X	X	X
Secondary Clinical Eye Exam Form	X			X	X				X	X
Visual Acuity Form	X		X	(x)	X			X	(x)	X
OCT Form	X		X	(x)	X			X	(x)	X
Fundus Form	X			(x)	X				(x)	X
Laboratory Report Form	X	X	X	(x)	X		X	X	(x)	X
Adverse Event Checklist		X	X	X	X	X	X	X	X	X
Vision Related Quality of Life	X			X	X				X	X
Health Related Quality of Life	X			X	X				X	X
Treatment Assessment Form	X	X	X	X	X	X	X	X	X	X
Patient Calendar***		X	X	X	X		X	X	X	X
Medication Log	X	X	X	X	X	X	X	X	X	X
Patient Dropout	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Protocol Deviation Form	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Adverse Event Narrative	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Adverse Event Log	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)

***Note that treatment failure may be declared at a scheduled study visit or at a non-study visit;**
All (x) are only to be filled out if applicable.
****If not switching on the same day as Phase I treatment failure**
*****Patients will complete this form and bring to the study coordinator for review**

4.3. Phase I Enrollment/Baseline visit

The Phase I Enrollment/Baseline visit should occur after the patient has been screened and determined to be eligible for the study. Screening is a process that should occur before or on the date of the patient's Enrollment/Baseline visit. The baseline eye exam and other baseline assessments may be collected at a separate visit up to 14 days *before* the patient is enrolled and randomized, with the exception of laboratory measurements which may be collected within 4 weeks or 90 days prior to or on the date of randomization (depending on the test).

Many patients will still have active enough inflammation at the time of enrollment to meet criteria (≥1+ AC cells, ≥1+ vitreous haze by NEI scale, or active retinal/choroidal inflammation). However, some patients may have had active inflammation when screened (within 14 days prior to enrollment) but at the time of enrollment, the inflammation is improved because of steroid treatment. As long as the inflammation met inclusion criteria within this 14 day period, those values can be used for the baseline exam (enrollment exam). If there is a patient whom you think is very likely to be enrolled in the next 14 days but you are still waiting for some screening labs, it is fine to go ahead and consent and obtain the baseline study assessments (eye exam with secondary grader using both NEI and Miami scales for vitreous haze, fundus photos, OCT, questionnaires, etc.), as long as you do not randomize. Randomization can only occur once all eligibility criteria have been verified. The inflammation recorded on the baseline Clinical Eye Exam form needs to meet inflammation eligibility criteria.

4.3.1. Consent and eligibility evaluation

Procedures for obtaining consent include explaining the patient's disease, prognosis, and treatment options, discussing the risks and benefits of participation, and addressing the patient's questions and concerns. After explaining the nature of the study and the rights and responsibilities of the patient, the ophthalmologist and/or the study coordinator will obtain written consent from the subject, or written minor assent and parental consent if applicable. The subject is assured that participation in this study is voluntary and he/she can withdraw at any time if he/she feels uncomfortable.

The eligibility evaluation will be performed using the Eligibility Form, which is to be filled out at the Baseline-I visit. For detailed inclusion/exclusion criteria please see Section 2.3.

There is not a mandated separate visit for eligibility screening. If the patient fulfills all eligibility and exclusion criteria on a visit, he/she may sign the consent form and be randomized at the beginning of the official Baseline-I visit. Note that this requires that the patient have laboratory results that are current according to inclusion criteria guidelines.

In some cases, partial eligibility will be confirmed on a screening visit but more information may be needed (such as laboratory confirmation of acceptable values of the CBC, AST, ALT and creatinine). If and when the laboratory results meet eligibility criteria, the patient will then be asked to complete a consent form, followed by randomization and the official Baseline-I visit. All other criteria must be met at the time the consent form is signed and randomization occurs (except the active inflammation criteria which must be met within 14 days prior to randomization).

4.3.2. Randomization

Randomization treatment assignment takes place during the Baseline-I visit after eligibility has been determined and the consent forms have been signed by the patient. In some cases randomization can occur on the same day that patient is screened for enrollment, if the patient signs the consent form on that day. If the patient wishes to come back at a later time to sign the consent forms, randomization will occur on the date they return. If a patient returns to sign the consent and enroll on a different date to his or her screening visit, he or she must have had the relevant laboratory tests within 4 weeks prior to enrollment for trial eligibility.

After obtaining the written consent, the study coordinator will assign the next identification number from the patient ID list. The coordinator will then log into the REDCap database to perform the randomization for the corresponding patient ID. The coordinator will take note of the treatment assigned by REDCap, dispense the assigned treatment to the patient, and review dosing instructions with the patient.

4.3.3. Procedures for data collection

Required study procedures include the following:

- Medical and Treatment History
- Clinical eye exam
- Visual acuity exam
- Optical Coherence Tomography (OCT)
- Fundus photography
- Laboratory measurements
- Health-related quality of life questionnaire
- Vision-related quality of life questionnaire(s)

4.3.4. Specimens

The following specimens will be collected for laboratory measurements *within 4 weeks prior to enrollment*:

- Blood for complete blood count (CBC with differential, limited to percentages of neutrophils and lymphocytes)
- Blood for CD4 at [redacted] sites only
- Blood for serum chemistry panel (AST, ALT, creatinine)
- Blood or urine pregnancy test (all female patients, excluding those that are post-menopausal)

The following specimens will be collected for laboratory measurements *within 90 days prior to enrollment*:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis C antibody
- Tuberculin skin test
- Interferon gamma release assay
- Chest radiograph
- Syphilis (RPR/VDRL/other non-specific)
- Syphilis (FTA-ABS/MHATP/other specific)

4.3.5. Forms for data collection

The following forms will be filled out as part of the Baseline-I visit:

- Patient Consent Forms
- Eligibility/Screening Form
- Baseline History Form
- Clinical Eye Exam Form
- Secondary Clinical Eye Exam Form
- Right Eye Visual Acuity Form
- Left Eye Visual Acuity Form
- OCT Form
- Fundus Photography Form
- Laboratory Report Form
- Quality of Life Questionnaire Forms
- Treatment Assessment Form
- Protocol Deviation Form (if applicable)

4.4. Follow-up visits

It is strongly encouraged for all follow up data to be collected within the study visit window, but should be collected regardless.

All Phase II procedures and protocol are the same as Phase I. For Phase I patients who are continuing on the same medication, physicians can see the patients as often as they would like. However, for purposes of this study we will only be recording information at Month 9 and Month 12, or a non-study visit that leads to treatment failure.

Laboratory test results will be collected monthly.

4.4.1. Procedures for data collection

Required study procedures include the following:

- Clinical eye exam
- Secondary Clinical eye exam*
- Visual acuity exam
- Optical Coherence Tomography
- Fundus Photography*
- Laboratory measurements
- Quality of Life Questionnaire Forms*

*Phase 1: treatment failure and 6 month visit (whichever is first), 12 month visit; Phase 2: treatment failure and 6 month visit.

4.4.2. Specimens

The following specimens will be collected for laboratory measurements:

- Blood for complete blood count (CBC with differential, limited to percentages of neutrophils and lymphocytes)
- Blood for CD4 at [redacted] sites only at Baseline, Month 3, 6, &12
- Blood for serum chemistry panel (AST, ALT, creatinine)
- Blood or urine pregnancy test (all female patients, excluding those that are post- menopausal)

4.4.3. Forms for data collection

The following forms will be filled out as part of the follow-up visits:

- Clinical Eye Exam Form
- Secondary Clinical Eye Exam Form*
- Right Eye Visual Acuity Form
- Left Eye Visual Acuity Form
- OCT Form
- Fundus Photography Form*
- Laboratory Report Form
- Adverse Event Checklist
- Medication Log
- Patient Medication Calendar (to be completed by the patient)
- Treatment Assessment Form
- *Adverse Event Log (update if necessary)*
- *Quality of Life Questionnaire Forms **
- *Serious Adverse Event Narrative Form (if applicable)*
- *Patient Dropout Form (if applicable)*
- *Protocol Deviation Form (if applicable)*

*Phase 1: baseline, treatment failure and 6 month visit, 12 month visit; Phase 2: treatment failure and 6 month visit; Treatment failure anytime (study or non-study visit)

For follow-up visits, all the above procedures and forms should be completed for all patients, regardless of if they are taking the medication or compliant with study visits.

4.5. Baseline Phase II

This visit may occur on the same day as treatment failure in Phase I, if the patient proceeds directly to Phase II. If both visits occur on the same day, study coordinators will mark the Phase I visit and Phase II visit at the same time on the case report forms. However, patients have up to two weeks to come back to clinic and begin Phase II after treatment failure in Phase I. In this case, complete the Baseline Phase II form packet on the date Baseline II starts.

4.5.1. Eligibility

In Phase I, if failure is due to efficacy or tolerability or for selected cases for safety (if deemed safe by the Medical Monitor), the patient will be considered as eligible for Phase II of the study. If there is a serious adverse event in Phase I, deemed to be related to the study drug by the Medical Monitor, the patient will be declared a treatment failure. The Medical Monitor will determine if it is safe for the patient to enter Phase II. If not, the patient should still be followed for 6 months.

As in Phase I, there is no mandated separate visit for eligibility screening in Phase II. If the patient is declared a treatment failure in Phase I for any reason other than an SAE deemed to be related to the study drug (by the Medical Monitor), he/she may immediately proceed to Phase II. Any reason for eligibility failure for Phase II will be captured in the adverse event log of the last Phase I visit, thus there is no need to have a separate eligibility screening form.

4.6. Non-study visits

Despite frequent study visits, some patients may need additional visits with their ophthalmologist according to standard of care that do not fall within study visit windows. Required data collection during these non-study visits is limited to adverse event reporting and declaration of treatment failure if it occurs. It is preferable that treatment failure is declared at a regularly scheduled study visit rather than a non-study visit, however if it is necessary the physician can decide to do so.

4.6.1. Study Procedures

Every attempt should be made to obtain all study procedures at a non-study visit if treatment failure is being declared. However, if this is not possible the required study procedures include the following:

- Clinical eye exam (if treatment failure is declared)

4.6.2. Specimens

No specimens are required during non-study visits.

4.6.3. Forms for data collection

The following forms will be filled out at non-study visits *only if treatment failure is declared.* Every attempt should be made to acquire information for all other forms. However, if this is not possible, at the minimum the following must be completed:

- Clinical Eye Exam Form
- Treatment Assessment Form
- Quality of Life
- Medication Log
- Adverse Event Checklist
- *Adverse Event Log (update if necessary)*
- *Serious Adverse Event Narrative Form (if applicable)*

5. Study examinations and procedures

5.1. Quality of life questionnaire administration

All patients will be asked to complete standard quality of life questionnaires related to overall health and visual function at baseline visits as well as at 6 months or treatment failure (whichever is first) in order to measure quality of life outcomes. Patients who experience treatment success with Phase I treatment and continue into Phase I (6-12 months) also complete questionnaires at the 12-month visit, or earlier if treatment failure is declared. The following questionnaires will be administered:

If treatment failure occurs prior to 6 months (Phase I and Phase II) questionnaires should also be collected at the time of treatment failure as well as 6 months.

Health-related quality of life

• SF-36 questionnaire (all patients)

Vision-related quality of life

- NEI-VFQ-25 (all patients)
- IND-VFQ (Indian patients only)

Given data suggesting that SF-36 scores vary by method of administration such that patients overstate their quality of life in clinic interviews, questionnaires will be self-administered whenever possible at clinic appointments. Additionally the NEI-VFQ should be self-administered whenever possible. It is anticipated that some patients will not have adequate visual function to complete the questionnaires on their own, and some patients may also be illiterate. In such cases, the coordinator will read the questions aloud to the patient and record the patient's answers on the appropriate questionnaire forms (Section A.13). It is very important that the questions are answered in their original form, so coordinators should never rephrase or interpret questions for the patient.

5.2.A Refraction and visual acuity (PRIMARY – FOR LETTER VISION CHARTS)

5.2.1.A Refraction procedure

Beginning Approximate Refraction

The beginning approximate refraction should be obtained by performing retinoscopy or auto- refraction. One of these measurements is used as the beginning approximate refraction at each visit.

Subjects who arrive for examination wearing contact lenses are asked to remove the lenses prior to refraction. The subject must wait for 30 minutes after removing the contact lenses before refraction can be performed.

Refraction may be initially performed at distances different than four meters (i.e. using a phoropter in a common refraction lane). However, if this is done, the spherical power refinement step must be repeated with lenses in place after the subject has been positioned at four meters for visual acuity testing.

The examiner will use Chart R (Precision Vision Chart Version 2110) for manifest refraction. Each eye is refracted at four meters unless the visual acuity measured at this distance on chart R is worse than 20/200 (defined as missing 2 or more letters on the top line, the 20/200 or 6/60 line). This subject must then be moved to a distance of one meter from the study visual acuity chart, and refraction must be performed and recorded at this distance.

Manifest Refraction

In general, instructions are to 'push plus' and to add minus diopter corrections only if there is a demonstrated increase in visual acuity, i.e., the patient is able to read more letters. The steps are as follows:

- Seat the subject 4 meters in front of the refraction chart;
- Place and adjust the trial frame on the subject's face so that the lens cells are parallel to the anterior plane of the orbit;
- Adjust the pupillary distance of the trial frame to make sure that the lenses position in front of the centers of the pupils;
- Adjust the lens cells for the proper distance from the cornea;
- Occlude the eye not being refracted;
- Insert spherical lens correction into the compartment closest to the eye;
- Place cylindrical lens correction in the compartment in the front of the frame;
- Set cylindrical lens to appropriate axis setting

Please refer to the table below to ensure that proper lenses are used for the appropriate visual acuity level:

Vision with Best Correction	**Sphere**		**Cylinder Use correct Jackson Cross Cylinder as below**			**Sphere Refinement**	
	Power	Increment	Axis	Power	Increment	Power	Increment
20/10-20/80	+0.50	+0.50	0.50	0.25	+0.25	+0.37	+0.25
6/3-6/24	- 0.37	- 0.25			-0.25	-0.37	-0.25
(4 meters)	+0.50	+0.50				+0.37	+0.25
20/100-20/200	+1.00	+1.00	1.00	1.00	+1.00	+0.50	+0.50
6/30-6/60	-1.00	-1.00			-1.00	-0.50	-0.50
(4 meters)	+1.00	+1.00				+0.50	+0.50
<20/200	+2.00	+2.00	1.00	1.00	+1.00	+1.00	+1.00
<6/60	-2.00	-2.00			-1.00	-1.00	-1.00
(1 meter)	+2.00	+2.00				+1.00	+1.00

Examples for each visual acuity level are detailed below.

<u>For Patients with Visual Acuity of 20/10-20/80 (6/3-6/24):</u>

Determine Sphere Power

- Ask patient to identify the smallest possible line that he/she can see on the Chart R;
- With the subject looking at the smallest line legible on the visual acuity chart, place a +0.50 spherical lens in front of the eye being tested. Ask the subject, "Is

vision better, worse, or the same?"

- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +0.50 more plus;
- Continue to check with the +0.50 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +0.50 lens makes the subject's vision worse, remove the +0.50 lens
- Then hold a -0.37 spherical lens over the eye;
- If this -0.37 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -0.25 more minus;
- Remember, if the patient reports that the -0.37 lens makes the vision better but if s/he is unable to read more letters, do not change spherical lens by -0.25.
- If the -0.37 spherical lens does not allow the patient to read more letters or if it makes the vision worse, recheck using the +0.50 lens
- If the +0.50 lens makes vision better or the same, repeat above sequence
- If the +0.50 lens makes vision worse, move on to cylindrical testing

Determine and refine cylinder axis

The following descriptions are for plus cylinders. Adjust accordingly for minus cylinder refraction.

- Ask the subject to look at a letter on a line of Chart R which is one line larger than the smallest line he/she could read (one above threshold);
- **If no cylinder** is present in the beginning approximate refraction, place the +/- 0.50 diopter cross-cylinder with the positive axis first at 90º and then at 180º, asking if either position makes the letter clearer;
- If the patient prefers either one of these positions, place a +0.50 cylindrical lens in the trial frame aligned with the preferred axis;
- If the patient did not prefer cylinder at axis 90° or 180°, position the cross cylinder with the positive axis first at 45° then 135°;
- Ask if the patient prefers either of these positions;
- If so, place a +0.50 cylinder lens in the trial frame aligned with the preferred axis;
- If the subject prefers none of the four positions, no further cylinder testing is required;
- **If cylinder is present** in the beginning approximate refraction **or if you have added +0.50 cylinder power in the above step**, position the +/- 0.50 diopter cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), and secondly with the positive axis at 45º to the left of the cylinder axis (position two). Ask the subject which position improves vision (position one or position two?);
- If the subject responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15º to the right or left and repeat;
- If the subject prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended (see Table below) and repeat. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

Table: Axis step sizes for refinement of cylinder.

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 to < 2.00 D	5°
2.00 to < 3.00 D	3°
3.00 to < 5.00 D	2°
5.00 to < 8.00 D	1°

Refine cylinder power

- Ask the subject to look at the lowest line on the visual acuity chart which can be read;
- Switch to +/- 0.25 diopter cross-cylinder;
- Align the ± 0.25 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better;
- If the subject prefers the negative axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by +0.25 diopter;
- If a subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90º away from the previous axis;
- If the subject prefers the positive axis coincident with the cylinder axis, increase the power of the trial frame by +0.25 diopter and retest;
- **Beginning with cylinder powers of 1.00 diopter or more, for each 0.5 diopter change in cylinder power, adjust the sphere power by 0.25 diopter of the opposite sign; this is done to maintain the spherical equivalent.**

Spherical refinement

End the refraction by performing the spherical refinement step.

- With the subject looking at the smallest line legible on the visual acuity chart, place a +0.37 spherical lens in front of the eye being tested. Ask the subject, "Is vision better, worse, or the same?"
- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +0.25 more plus;
- Continue to check with the +0.37 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +0.37 lens makes the subject's vision worse, remove the +0.37 lens;
- Then hold a -0.37 spherical lens over the eye;
- If this -0.37 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -0.25 more minus;
- Continue presenting the -0.37 lens to see if there is any further improvement in vision;
- When an additional -0.37 lens does not improve vision;
- Present the +0.37 lens, again asking "if vision is better, worse or the same?"
- If patient responds that vision is better or the same, repeat spherical refinement testing as detailed above;
- If patient responds that vision is worse, testing is complete.
- **Remember to always end the refraction by checking with plus lenses.**

For Patients with Visual Acuity of 20/100-20/200 (6/30-6/60):

Determine Sphere Power

- Ask patient to identify the smallest possible line that he/she can see on the Chart R;
- With the subject looking at the smallest line legible on the visual acuity chart, place a +1.00 spherical lens in front of the right eye. Ask the subject, "Is vision better, worse, or no change?"
- If the subject responds that vision is made better or is the same, replace the spherical lens with one that is +1.00 more plus;
- Continue to check with the +1.00 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +1.00 lens makes the subject's vision worse, remove the +1.00 lens
- Then hold a -1.00 spherical lens over the eye;
- If this -1.00 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -1.00 more minus;
- Remember, if the patient reports that the -1.00 lens makes the vision better but if s/he is unable to read more letters, do not change spherical lens by -1.00.
- If the -1.00 spherical lens does not allow the patient to read more letters or if it makes the vision worse, recheck using the +1.00 lens; recheck using +1.00 lens
- If the +1.00 lens makes vision better or the same, repeat above sequence
- If the +1.00 lens makes vision worse, move on to cylindrical testing;
- **NOTE:** if visual acuity improves significantly during manifest refraction, the examiner may need to change to trial lenses that are specified for the new level of acuity for the remainder of the refraction. Please refer to the Trial Lens Guide above.

Determine and refine cylinder axis

The following descriptions are for plus cylinders. Adjust accordingly for minus cylinder refraction.

- Ask the subject to look at a letter on a line of Chart R which is one line larger than the smallest line he/she could read (one above threshold);
- **If no cylinder** is present in the beginning approximate refraction, place the +/- 1.00 diopter cross-cylinder with the positive axis first at 90º and then at 180º, asking if either position makes the letter clearer;
- If the patient prefers either of these positions, place a +1.00 cylindrical lens in the trial frame at the preferred axis;
- If the patient did not prefer cylinder at axis 90° or 180°, position the cross cylinder with the positive axis first at 45° then 135°;
- Ask if the patient prefers either of these positions;
- If so, place a +1.00 cylinder lens in the trial frame at the preferred axis;
- If the subject prefers none of the four positions, no further cylinder testing is required;
- **If cylinder is present** in the beginning approximate refraction **or if you have added +1.00 cylinder power in the above step**, position the +/- 1.00 diopter cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), and secondly with the positive axis at 45º to the left of the cylinder axis (position two). Ask the subject which position improves the vision (position one or position two?);

- If the subject responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15º to the right or left and repeat;
- If the subject prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended (see Table below) and repeat. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

Table: Axis step sizes for refinement of cylinder

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 to < 2.00 D	5°
2.00 to < 3.00 D	3°
3.00 to < 5.00 D	2°
5.00 to < 8.00 D	1°

Refine cylinder power

- Ask the subject to look at the lowest line on the visual acuity chart which can be read;
- Align the ± 1.00 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better;
- If the subject prefers the negative axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by +1.00 diopter;
- If a subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90º away from the previous axis;
- If the subject prefers the positive axis coincident with the cylinder axis, increase the power of the trial frame by +1.00 diopter and retest;
- Beginning with cylinders of 1.00 diopter or more, for each 0.5 diopter change in cylinder power, adjust the sphere by 0.25 diopter of the opposite sign; this is done to maintain the spherical equivalent.

Spherical refinement

End the refraction by performing the spherical refinement step.

- With the subject looking at the smallest line legible on the visual acuity chart, place a +0.50 spherical lens in front of the eye being tested. Ask the subject, “Is vision better, worse, or the same?”
- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +0.50 more plus;
- Continue to check with the +0.50 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +0.50 lens makes the subject’s vision worse, remove the +0.50 lens
- Then hold a -0.50 spherical lens over the eye;
- If this -0.50 lens improves the subject’s vision, even by one letter, replace the spherical lens in the trial frame by one that is -0.50 more minus;
- Continue presenting the -0.50 lens to see if there is further improvement in vision;
- When an additional -0.50 lens does not improve vision;
- Show the patient the +0.50 lens, again asking “if vision is better, worse or the

same?"
- If patient responds that vision is better or the same, repeat spherical refinement testing as detailed above;
- If patient responds that vision is worse, refraction testing is complete.
- **Remember to always to end the refraction by checking with plus power.**

For Patients with Visual Acuity <20/200 (<6/60):

Determine Sphere Power

NOTE: **If refraction cannot be performed at 4 meters**, defined as missing 2 or more letters on the largest line, then the subject should be moved to 1 meter and the above refraction sequence followed. **At 1 meter, a + 0.75 spherical lens is added** to the beginning approximate refraction to adjust for the accommodative difference between 4 and 1 meter.

- Ask patient to identify the smallest possible line that he/she can see on the Chart R;
- With the subject looking at the smallest line legible on the visual acuity chart, place a +2.00 spherical lens in front of the right eye. Ask the subject, "Is it better, worse, or no change?"
- If the subject responds that vision is made better or is the same, replace the spherical lens with one that is +2.00 more plus;
- Continue to check with the +2.00 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +2.00 lens makes the subject's vision worse, remove the +2.00 lens
- Then hold a -2.00 spherical lens over the eye;
- If this -2.00 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -2.00 more minus;
- Remember, if the patient reports that the -2.00 lens makes the vision better but if s/he is unable to read more letters, do not change spherical lens by -2.00.
- If the -2.00 spherical lens does not allow the patient to read more letters or if it makes the vision worse, retest using +2.00 lens;If the +2.00 lens makes vision better or the same, repeat above sequence;
- If the +2.00 lens makes vision worse, move onto cylindrical testing;
- **NOTE:** if visual acuity improves significantly during manifest refraction, the examiner may need to change to trial lenses that are specified for the new level of acuity for the remainder of the refraction. Please refer to the Trial Lens Guide above.

Determine and refine cylinder axis

The following descriptions are for plus cylinders. Adjust accordingly for minus cylinder refraction.

- Ask the subject to look at a letter on a line of Chart R which is one line larger than the smallest line he/she could read (one above threshold);
- **If no cylinder** is present in the beginning approximate refraction, place the +/- 1.00 diopter cross-cylinder with the positive axis first at 90º and then at 180º, asking if either position makes the letters clearer;
- If the patient prefers either of these positions, place a +1.00 cylindrical lens in the trial frame at the preferred axis;
- If the patient did not prefer cylinder at axis 90° or 180°, position the cross

cylinder with the positive axis first at 45° then 135°;
- Ask if the patient prefers either of these positions;
- If so, place a +1.00 cylinder lens in the trial frame at the preferred axis;
- If the subject prefers none of the four positions, no further cylinder testing is required.
- **If cylinder is present** in the beginning approximate refraction **or if you have added +1.00 cylinder power in the above step**, position the +/- 1.00 diopter cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), and secondly with the positive axis at 45º to the left of the cylinder axis (position two). Ask the subject which position improves the vision (position one or position two?);
- If the subject responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15º to the right or left and repeat;
- If the subject prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended (see table below) and repeat. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

Table: Axis step sizes for refinement of cylinder

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 to < 2.00 D	5°
2.00 to < 3.00 D	3°
3.00 to < 5.00 D	2°
5.00 to < 8.00 D	1°

Refine cylinder power

- Ask the subject to look at the lowest line on the visual acuity chart which can be read;
- Align the ± 1.00 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better;
- If the subject prefers the negative axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by 1.00 diopter;
- If a subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90º away from the previous axis;
- If the subject prefers the positive axis coincident with the cylinder axis, increase the power of the trial frame by +1.00 diopter and retest;
- Beginning with cylinders of 1.00 diopter or more, for each 0.5 diopter change in cylinder power, adjust the sphere by 0.25 diopter of the opposite sign, this is done to maintain the spherical equivalent.

Spherical refinement

End the refraction by performing the spherical refinement step.
- With the subject looking at the smallest line legible on the visual acuity chart, place a +1.00 spherical lens in front of the eye being tested. Ask the subject, “Is

vision better, worse, or the same?"

- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +1.00 more plus;
- Continue to check with the +1.00 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +1.00 lens makes the subject's vision worse, remove the +1.00 lens
- Then hold a -1.00 spherical lens over the eye;
- If this -1.00 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -1.00 more minus;
- Continue presenting the -1.00 lens to see if there is further improvement in vision;
- When an additional -1.00 lens does not improve vision;
- Present the +1.00 lens, again asking "if vision is better, worse or the same?"
- If patient responds that vision is better or the same, repeat spherical refinement testing as detailed above;
- If patient responds that vision is worse, testing is complete.
- **Remember to always to end the refraction by checking with plus power.**

Record the lens correction obtained during manifest refraction for the right eye on the appropriate examination forms in the section for visual acuity measurements (Section A.5). Then proceed to refraction of the left eye, following steps as outlined above.

5.2.2.A Visual acuity procedure

Visual acuity measurement is necessary for a secondary outcome in this trial. Therefore, we have created a standardized method that aims to minimize any bias from either the examiner or the patient. This has been adapted from the Visual Acuity protocols from the Age Related Eye Disease Study (AREDS 1999)[32], and the Aravind Eye Hospital's Practical Guide to Refraction[33] and is similar to the method we are currently using at [redacted]

Visual Acuity Charts

The following equipment is used: a set of three charts, which are modified Bailey-Lovie charts, Charts 1, 2 and R (Precision Vision Chart 2110, 2111 and 2112, respectively). Each chart consists of 14 lines of high-contrast letters. There is a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution) from line to line.

Chart 1 is for measuring aided visual acuity of the right eye and Chart 2 is to be used for measuring aided visual acuity of the left eye at all visits. Chart R will be used for obtaining all manifest subjective refractions.

Visual Acuity Boxes

The dimensions of the light box are 24 and 3/4 inches (62.9 cm) by 25 and 3/4 inches (65.4 cm) by 7 inches (17.8 cm). The box can be mounted on a wall or on a cylindrical stand. The stand is mounted on a five-pronged wheelbase, with each prong about 14 inches (35.6 cm) long; two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied. The light box should be mounted at a height such that the top of the third row of letters (0.8 logMAR, 45 letters, 20/125 Snellen) is 49 +/- 2 inches (124.5 +/-5.1 cm) from the floor. The rear of the box provides storage space for the two charts not being used.

Illumination

The overhead room lights should be turned **off** during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect such as glare. With the box light off, not more than 15 foot-candles of light should fall on the center of the chart. The visual acuity light box is equipped with two **20- watt** fluorescent tubes. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2,000 hours, new tubes should be kept "on" for about 4 days (approximately 96 hours, does not have to be continuous) before use. All tubes should be replaced once a year.

Each tube is partially covered by a 14-inch (35.6 cm) fenestrated sleeve, open in the back, which serves as a baffle to reduce illumination. Each sleeve should be centered on the tube such that an equal length of tube (about 4 and 3/16 inches or 10.6 cm) is left uncovered to the right and left of the sleeve.

4- and 1-Meter Visual Acuity Lanes

A distance of 4 meters (13 feet and 1.5 inches, or 157.5 inches) is required between the subject's eyes and the visual acuity chart for the 4-meter test, and a distance of 1 meter (39 and 3/8 inches) is required for the 1-meter test. The room for visual acuity testing must have, in addition to the 4- meter lane, space for the visual acuity box (and possibly a stand) and space for the subject.

- Wall-mounted box: In addition to the 4-meter lane, 7 inches (17.8 cm) must be allowed for the depth of the box plus space for the subject to sit or stand.
- Stand-mounted box: In addition to the 4-meter lane, 13 inches (33 cm) must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the subject to sit or stand.

Marking the Distance

4 Meters

- If the chair and visual acuity box are permanently affixed, distance measurements need to be made only once and no floor marks are needed to ensure the correct distance.
- If the box is mounted on the wall but the subject's chair is not permanently affixed, the 4- meter distance of the subject's eye from the chart must be marked clearly and permanently.
- If the box is mounted on a movable stand, the 4-meter distance must be marked clearly and permanently. The location and orientation of the box must be rechecked each time a new chart is put in place or the box is touched. When the stand touches the rear wall of the room, two of the five casters should touch the wall.

1 Meter

- The 1-meter distance is measured from the eye of the subject, who is seated comfortably in a chair with his or her back firmly placed against the chair's back, to the center of the second (for testing the left eye) or fourth letter (for testing the right eye) of the third line of the chart. A stick, one meter long, should be used to confirm the distance for each subject.

Visual Acuity Procedure

- Visual acuity will be measured at each study visit.
- Visual acuity should be measured for each eye AFTER refraction. Visual acuity should NOT be recorded during the refraction procedure.
- It is very important that the examiner is not aware of the patient's clinical records, in order to minimize bias. Therefore, the visual acuity examiner will not have access to the patient's previous clinical examination or treatment results.
- Visual acuity is tested separately for each eye (one eye at a time). The patient's untested eye will be completely covered with a patch, to block out all light from entering this eye. The examiner must constantly ensure that this eye remains occluded at all times.
- The patient is instructed to read each letter on the chart starting with the largest line, at the 4-meter distance, and is encouraged to read as many letters as possible.
- If the patient cannot identify a letter, they are encouraged to guess. **Only one response is allowed per letter**.
- The examiner must ensure that the patient does not squint (creating a pin-hole effect) or lean forward (reducing the distance to the chart).
- Once a patient has given a response for a letter and has moved on to provide a response for the next letter, any corrections of previous response will not be accepted.
- However, if the patient has given a response for a letter and has not yet moved on to provide a response for the next letter, a correction of the previous response is accepted.
- If the subject gives two possible responses for a letter, tell the patient to commit to one answer. **The examiner CANNOT, at any time, give the patient any indication as to whether a response is correct or incorrect.**
- In the case that the patient reads less than 20 letters at 4 meters, move the patient or the chart so that there is a distance between the two of 1 meter.
- Visual acuity will then be retested at this 1 meter distance.
- Only the first 6 rows of letters need to be read at 1 meter.
- If no letters are read at 1 meter, then the examiner must proceed to Low Vision Testing (see below), starting with Count Fingers testing. If the patient does not adequately Count Fingers, proceed to Hand Motion. If the patient does not adequately recognize Hand Motion, then proceed to Light Perception.

Testing of Count Fingers Vision

In testing for count fingers vision, the examiner's hand presenting 1, 2, or 5 fingers is held steady at a distance of 1 meter directly in front of the eye being examined. The fellow eye is completely occluded with a patch. Refractive correction should not be used. A light should be shown directly on the hand from behind the subject and room lights should be turned on. The examiner's fingers should be presented in random order and repeated 5 times. Eccentric viewing should be encouraged. If the subject correctly identifies three of the five presentations, then count fingers visions is noted. If not, then the subject must be tested for hand motion vision.

Testing of Hand Motion Vision

The examiner's hand with all fingers spread out should be extended ½ meter directly in front of the eye being examined. The fellow eye should be occluded with a patch.

Refractive correction should not be used. A light should be shone directly on the hand from behind the subject and room lights should be turned on. The examiner's hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per second. The subject is instructed that the examiner's hand will be presented and they will have to respond to the question: "What am I doing with my hand?" This should be repeated five times. Four out of five correct responses indicate that hand motions visions is present. If the subject does not correctly identify four out of five, then you must test for light perception.

Testing for Light Perception

The indirect ophthalmoscope is used as the light source for testing light perception. Room lights should be off. The opposite eye must be completely patched. No correction should be used. From a distance of ½ meter with the light source turned up to maximum intensity, the light from the indirect ophthalmoscope is directed into the subject's eye four times. The subject is asked to respond when the light is "on". Light Perception is recorded if the examiner is convinced the subject sees the light. Otherwise, the vision should be recorded as "No Light Perception".

Scoring Best Corrected Visual Acuity

On the Visual Acuity Forms, the examiner will circle all letters read correctly. Letters read incorrectly or not read at all will be left unmarked. At the end of each row of letters, the examiner will write down the total number of letters read correctly on the line provided. If visual acuity was not tested at 1 meter, the examiner will indicate this on the form.

After each measurement of visual acuity, the biostatistician will calculate the score for the visit.

The Snellen equivalent, defined as the Snellen ratio corresponding to the most difficult line for which the subject read at least 4 of 5 letters correctly, will also be entered by the examiner on the 4-meter Visual Acuity Form (Section A.5).
The data entry staff will enter the number correct on each row at 4 meters, and if applicable, 1 meter and low vision testing results (They will not enter which letters the examiner circled, i.e., which letters the patient identified correctly.). Coordinating center personnel will double check the data entered by the examiner and data entry staff.

5.2.3.A Visual acuity training and certification

The goal of the certification process is to standardize methodology for refraction and visual acuity measurement. All visual function examinations must be performed by study-certified technicians. The principal investigator at each site is responsible for ensuring that the appropriate personnel are identified, trained and certified. A qualified visual function examiner (SL) from the Clinical Coordinating Center ([redacted]) will certify the rooms and technicians at each site.

Technicians are expected to perform the refraction and visual acuity tests on at least one and possibly more non-study subjects according to protocol requirements. The examiner will determine whether or not the candidate executes the study protocol accurately for each procedure. A checklist (Visual Acuity/Refraction Certification Form, Section B.1) containing required procedures will be used to facilitate this process.

Room certification will be performed and recorded (Room Certification Form, section B.2) to ensure that all study rooms meet illumination, equipment, and distance requirements. Logs should be kept to document dates of light box bulb replacement.

Certification is valid for a period 18 months (± 2 months) from the date of certification. The process should begin as soon as possible, as technicians must be certified before the first study subject is seen. **A minimum of two certified technicians** are required at each site. The visual acuity measurement schedule may be found on the Study Forms Completion Schedule.

5.2.B Refraction and visual acuity (PROTOCOL FOR TUMBLING E CHART)

5.2.1.B Refraction procedure

Beginning Approximate Refraction

The beginning approximate refraction should be obtained by performing retinoscopy or auto- refraction. One of these measurements is used as the beginning approximate refraction at each visit.
Subjects who arrive for examination wearing contact lenses are asked to remove the lenses prior to refraction. The subject must wait for 30 minutes after removing the contact lenses before refraction can be performed.

Refraction may be initially performed at distances different than four meters (i.e. using a phoropter in a common refraction lane). However, if this is done, the spherical power refinement step must be repeated with lenses in place after the subject has been positioned at four meters for visual acuity testing.

The examiner will use Chart R (Precision Vision Chart Version 2305b) for manifest refraction. Each eye is refracted at four meters unless the visual acuity measured at this distance on chart R is worse than 20/200 (defined as missing 2 or more letters on the top line, the 20/200 or 6/60 line). This subject must then be moved to a distance of one meter from the study visual acuity chart, and refraction must be performed and recorded at this distance. Use of Visual Acuity Form R is optional but may be helpful in keeping track of patient's acuity level.

Manifest Refraction

In general, instructions are to 'push plus' and to add minus diopter corrections only if there is a demonstrated increase in visual acuity, i.e., the patient is able to read more letters. The steps are as follows:

- Seat the subject 4 meters in front of the refraction chart;
- Place and adjust the trial frame on the subject's face so that the lens cells are parallel to the anterior plane of the orbit;
- Adjust the pupillary distance of the trial frame to make sure that the lenses position in front of the centers of the pupils;
- Adjust the lens cells for the proper distance from the cornea;
- Occlude the eye not being refracted;
- Insert spherical lens correction into the compartment closest to the eye;
- Place cylindrical lens correction in the compartment in the front of the frame;
- Set cylindrical lens to appropriate axis setting

Please refer to the table below to ensure that proper lenses are used for the appropriate visual acuity level:

Vision with Best Correction	**Sphere**		**Cylinder Use correct Jackson Cross Cylinder as below**			**Sphere Refinement**	
	Power	Increment	Axis	Power	Increment	Power	Increment
6/3-6/24	+0.50	+0.50	0.50	0.25	+0.25	+0.37	+0.25
20/10-20/80	-0.37	-0.25			-0.25	-0.37	-0.25
(4 meters)	+0.50	+0.50				+0.37	+0.25
6/30-6/60	+1.00	+1.00	1.00	1.00	+1.00	+0.50	+0.50
20/100-20/200	-1.00	-1.00			-1.00	-0.50	-0.50
(4 meters)	+1.00	+1.00				+0.50	+0.50
<6/60	+2.00	+2.00	1.00	1.00	+1.00	+1.00	+1.00
<20/200	-2.00	-2.00			-1.00	-1.00	-1.00
(1 meter)	+2.00	+2.00				+1.00	+1.00

Examples for each visual acuity level are detailed below.

For Patients with Visual Acuity of 6/3-6/24 (20/10-20/80):

Determine Sphere Power

- Ask patient to identify the orientation of the tumbling “E”s on the smallest possible line that he/she can see on the Chart R;
- With the subject looking at the smallest line legible on the visual acuity chart, place a +0.50 spherical lens in front of the eye being tested. Ask the subject, “Is vision better, worse, or the same?”
- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +0.50 more plus;
- Continue to check with the +0.50 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +0.50 lens makes the subject’s vision worse, remove the +0.50 lens
- Then hold a -0.37 spherical lens over the eye;
- If this -0.37 lens improves the subject’s vision, even by one letter, replace the spherical lens in the trial frame by one that is -0.25 more minus;
- Remember, if the patient reports that the -0.37 lens makes the vision better but if s/he is unable to read more letters, do not change spherical lens by -0.25.
- If the -0.37 spherical lens does not allow the patient to read more letters or if it makes the vision worse, retest using the +0.50 lens;
- If the +0.50 lens makes vision better or the same, repeat above sequence
- If the +0.50 lens makes vision worse, move on to cylindrical testing

Determine and refine cylinder axis

The following descriptions are for plus cylinders. Adjust accordingly for minus cylinder refraction.

- Ask the subject to look at a letter on a line of Chart R which is one line larger than the smallest line he/she could read (one above threshold);
- **If no cylinder** is present in the beginning approximate refraction, place the +/- 0.50 diopter cross-cylinder with the positive axis first at 90º and then at 180º,

asking if either position makes the letters clearer;

- If the patient prefers either one of these positions, place a +0.50 cylindrical lens in the trial frame aligned with the preferred axis;
- If the patient did not prefer cylinder at axis 90° or 180°, position the cross cylinder with the positive axis first at 45° then 135°;
- Ask if the patient prefers either of these positions;
- If so, place a +0.50 cylinder lens in the trial frame aligned with the preferred axis;
- If the subject prefers none of the four positions, no further cylinder testing is required;
- **If cylinder is present** in the beginning approximate refraction **or if you have added +0.50 cylinder power in the above step**, position the +/- 0.50 diopter cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), and secondly with the positive axis at 45º to the left of the cylinder axis (position two). Ask the subject which position improves vision (position one or position two?);
- If the subject responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15º to the right or left and repeat;
- If the subject prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended (see Table below) and repeat. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

Table: Axis step sizes for refinement of cylinder.

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 to < 2.00 D	5°
2.00 to < 3.00 D	3°
3.00 to < 5.00 D	2°
5.00 to < 8.00 D	1°

Refine cylinder power

- Ask the subject to look at the lowest line on the visual acuity chart which can be read;
- Switch to +/- 0.25 diopter cross-cylinder;
- Align the ± 0.25 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better;
- If the subject prefers the negative axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by +0.25 diopter;
- If a subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90º away from the previous axis;
- If the subject prefers the positive axis coincident with the cylinder axis, increase the power of the trial frame by +0.25 diopter and retest;
- **Beginning with cylinder powers of 1.00 diopter or more, for each 0.5 diopter change in cylinder power, adjust the sphere power by 0.25 diopter of the opposite sign; this is done to maintain the spherical equivalent.**

Spherical refinement

End the refraction by performing the spherical refinement step.

- With the subject looking at the smallest line legible on the visual acuity chart, place a +0.37 spherical lens in front of the eye being tested. Ask the subject, "Is vision better, worse, or the same?"
- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +0.25 more plus;
- Continue to check with the +0.37 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +0.37 lens makes the subject's vision worse, remove the +0.37 lens;
- Then hold a -0.37 spherical lens over the eye;
- If this -0.37 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -0.25 more minus;
- Continue presenting the -0.37 lens to see if there is any further improvement in vision;
- When an additional -0.37 lens does not improve vision;
- Present the +0.37 lens, again asking "if vision is better, worse or the same?"
- If patient responds that vision is better or the same, repeat spherical refinement testing as detailed above;
- If patient responds that vision is worse, testing is complete.
- **Remember to always to end the refraction by checking with plus lenses.**

For Patients with Visual Acuity of 6/30-6/60 (20/100-20/200):

Determine Sphere Power

- Ask patient to identify the orientation of the tumbling "E"s on the smallest possible line that he/she can see on the Chart R;
- With the subject looking at the smallest line legible on the visual acuity chart, place a +1.00 spherical lens in front of the right eye. Ask the subject, "Is vision better, worse, or no change?"
- If the subject responds that vision is made better or is the same, replace the spherical lens with one that is +1.00 more plus;
- Continue to check with the +1.00 lens to see if the subject will accept more plus by repeating the step above;
- If an additional +1.00 lens makes the subject's vision worse, remove the +1.00 lens
- Then hold a -1.00 spherical lens over the eye;
- If this -1.00 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -1.00 more minus;
- Remember, if the patient reports that the -1.00 lens makes the vision better but if s/he is unable to read more letters, do not change spherical lens by -1.00.
- If the -1.00 spherical lens does not allow the patient to read more letters or if it makes the vision worse, retest using the +0.50 lens;
- If the +1.00 lens makes vision better or the same, repeat above sequence;
- If the +1.00 lens makes vision worse, move on to cylindrical testing;
- **NOTE:** if visual acuity improves significantly during manifest refraction, the examiner may need to change to trial lenses that are specified for the new level of acuity for the remainder of the refraction. Please refer to the Trial Lens Guide above.

Determine and refine cylinder axis

The following descriptions are for plus cylinders. Adjust accordingly for minus cylinder refraction.

- Ask the subject to look at a letter on a line of Chart R which is one line larger

than the smallest line he/she could read (one above threshold);

- **If no cylinder** is present in the beginning approximate refraction, place the +/- 1.00 diopter cross-cylinder with the positive axis first at 90º and then at 180º, asking if either position makes the letters clearer;
- If the patient prefers either of these positions, place a +1.00 cylindrical lens in the trial frame at the preferred axis;
- If the patient did not prefer cylinder at axis 90° or 180°, position the cross cylinder with the positive axis first at 45° then 135°;
- Ask if the patient prefers either of these positions;
- If so, place a +1.00 cylinder lens in the trial frame at the preferred axis;
- If the subject prefers none of the four positions, no further cylinder testing is required;
- **If cylinder is present** in the beginning approximate refraction **or if you have added +1.00 cylinder power in the above step**, position the +/- 1.00 diopter cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), and secondly with the positive axis at 45º to the left of the cylinder axis (position two). Ask the subject which position improves the vision (position one or position two?);
- If the subject responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15º to the right or left and repeat;
- If the subject prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended (see Table below) and repeat. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

Table: Axis step sizes for refinement of cylinder

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 to < 2.00 D	5°
2.00 to < 3.00 D	3°
3.00 to < 5.00 D	2°
5.00 to < 8.00 D	1°

Refine cylinder power

- Ask the subject to look at the lowest line on the visual acuity chart which can be read;
- Align the ± 1.00 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better;
- If the subject prefers the negative axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by +1.00 diopter;
- If a subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90º away from the previous axis;
- If the subject prefers the positive axis coincident with the cylinder axis, increase the power of the trial frame by +1.00 diopter and retest;
- Beginning with cylinders of 1.00 diopter or more, for each 0.5 diopter change in cylinder power, adjust the sphere by 0.25 diopter of the opposite sign; this is done to maintain the spherical equivalent.

Spherical refinement

End the refraction by performing the spherical refinement step.

- With the subject looking at the smallest line legible on the visual acuity chart, place a +0.50 spherical lens in front of the eye being tested. Ask the subject, "Is vision better, worse, or the same?"
- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +0.50 more plus;
- Continue to check with the +0.50 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +0.50 lens makes the subject's vision worse, remove the +0.50 lens
- Then hold a -0.50 spherical lens over the eye;
- If this -0.50 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -0.50 more minus;
- Continue presenting the -0.50 lens to see if there is further improvement in vision;
- When an additional -0.50 lens does not improve vision;
- Show the patient the +0.50 lens, again asking "if vision is better, worse or the same?"
- If patient responds that vision is better or the same, repeat spherical refinement testing as detailed above;
- If patient responds that vision is worse, refraction testing is complete.
- **Remember to always to end the refraction by checking with plus power.**

For Patients with Visual Acuity < 6/60 (<20/200):

Determine Sphere Power

NOTE: **If refraction cannot be performed at 4 meters**, defined as missing 2 or more letters on the largest line, then the subject should be moved to 1 meter and the above refraction sequence followed. **At 1 meter, a + 0.75 spherical lens is added** to the beginning approximate refraction to adjust for the accommodative difference between 4 and 1 meter.

- Ask patient to identify the orientation of the tumbling "E"s on the smallest possible line that he/she can see on the Chart R;
- With the subject looking at the smallest line legible on the visual acuity chart, place a +2.00 spherical lens in front of the right eye. Ask the subject, "Is it better, worse, or no change?"
- If the subject responds that vision is made better or is the same, replace the spherical lens with one that is +2.00 more plus;
- Continue to check with the +2.00 lens to see if the subject will accept more plus by repeating the step above;
- If an additional +2.00 lens makes the subject's vision worse, remove the +2.00 lens
- Then hold a -2.00 spherical lens over the eye;
- If this -2.00 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -2.00 more minus;
- Remember, if the patient reports that the -2.00 lens makes the vision better but if s/he is unable to read more letters, do not change spherical lens by -2.00.
- If the -2.00 spherical lens does not allow the patient to read more letters or if it makes the vision worse, retest using the +2.00 lens;
- If the +2.00 lens makes vision better or the same, repeat above sequence;
- If the +2.00 lens makes vision worse, move on to cylindrical testing;

- **NOTE:** if visual acuity improves significantly during manifest refraction, the examiner may need to change to trial lenses that are specified for the new level of acuity for the remainder of the refraction. Please refer to the Trial Lens Guide above.

Determine and refine cylinder axis

The following descriptions are for plus cylinders. Adjust accordingly for minus cylinder refraction.

- Ask the subject to look at a letter on a line of Chart R which is one line larger than the smallest line he/she could read (one above threshold);
- **If no cylinder** is present in the beginning approximate refraction, place the +/- 1.00 diopter cross-cylinder with the positive axis first at 90º and then at 180º, asking if either position makes the letters clearer;
- If the patient prefers either of these positions, place a +1.00 cylindrical lens in the trial frame at the preferred axis;
- If the patient did not prefer cylinder at axis 90° or 180°, position the cross cylinder with the positive axis first at 45° then 135°;
- Ask if the patient prefers either of these positions;
- If so, place a +1.00 cylinder lens in the trial frame at the preferred axis;
- If the subject prefers none of the four positions, no further cylinder testing is required.
- **If cylinder is present** in the beginning approximate refraction **or if you have added +1.00 cylinder power in the above step**, position the +/- 1.00 diopter cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), and secondly with the positive axis at 45º to the left of the cylinder axis (position two). Ask the subject which position improves the vision (position one or position two?);
- If the subject responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder in the trial frame 15º to the right or left and repeat;
- If the subject prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended (see table below) and repeat. (If the subject states that one position of the cross-cylinder is no better than the other position, proceed to refining cylinder power).

Table: Axis step sizes for refinement of cylinder

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 to < 2.00 D	5°
2.00 to < 3.00 D	3°
3.00 to < 5.00 D	2°
5.00 to < 8.00 D	1°

Refine cylinder power

- Ask the subject to look at the lowest line on the visual acuity chart which can be read;
- Align the ± 1.00 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the subject which is better;
- If the subject prefers the negative axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by 1.00 diopter;
- If a subject indicates a change that would introduce negative cylinder power,

remove all cylinder power and continue testing for positive cylinder power at an axis 90° away from the previous axis;
- If the subject prefers the positive axis coincident with the cylinder axis, increase the power of the trial frame by +1.00 diopter and retest;
- Beginning with cylinders of 1.00 diopter or more, for each 0.5 diopter change in cylinder power, adjust the sphere by 0.25 diopter of the opposite sign, this is done to maintain the spherical equivalent.

Spherical refinement

End the refraction by performing the spherical refinement step.
- With the subject looking at the smallest line legible on the visual acuity chart, place a +1.00 spherical lens in front of the eye being tested. Ask the subject, "Is vision better, worse, or the same?"
- If the subject responds that vision is made better or if there is no change, replace the spherical lens with one that is +1.00 more plus;
- Continue to check with the +1.00 lens to see if the subject will accept more plus by repeating the step above;
- When an additional +1.00 lens makes the subject's vision worse, remove the +1.00 lens
- Then hold a -1.00 spherical lens over the eye;
- If this -1.00 lens improves the subject's vision, even by one letter, replace the spherical lens in the trial frame by one that is -1.00 more minus;
- Continue presenting the -1.00 lens to see if there is further improvement in vision;
- When an additional -1.00 lens does not improve vision;
- Present the +1.00 lens, again asking "if vision is better, worse or the same?"
- If patient responds that vision is better or the same, repeat spherical refinement testing as detailed above;
- If patient responds that vision is worse, testing is complete.
- **Remember to always to end the refraction by checking with plus power.**

Record the lens correction obtained during manifest refraction for the right eye on the appropriate examination forms in the section for visual acuity measurements (Section A.5). Then proceed to refraction of the left eye, following steps as outlined above.

5.2.2.B Visual acuity procedure

Visual acuity measurement is necessary for a secondary outcome in this trial. Therefore, we have created a standardized method that aims to minimize any bias from either the refractionist or the patient. This has been adapted from the Visual Acuity protocols from the Age Related Eye Disease Study (AREDS 1999)[32], and the Aravind Eye Hospital's Practical Guide to Refraction[33] and is similar to the method we are currently using at [redacted].

Visual Acuity Charts

The following equipment is used: a set of three charts, which are modified Bailey-Lovie charts, Charts 1, 2 and R (Precision Vision Chart 2305, 2305a and 2305b, respectively). Each chart consists of 14 lines of high-contrast "tumbling E's". There is a geometric progression of letter size (and, thus, an arithmetic progression of the logarithm of minimum angle of resolution) from line to line.

Chart 1 is for measuring aided visual acuity of the right eye and Chart 2 is to be used for

measuring aided visual acuity of the left eye at all visits. Chart R will be used for obtaining all manifest subjective refractions.

Visual Acuity Boxes

The dimensions of the light box are 24 and 3/4 inches (62.9 cm) by 25 and 3/4 inches (65.4 cm) by 7 inches (17.8 cm). The box can be mounted on a wall or on a cylindrical stand. The stand is mounted on a five-pronged wheelbase, with each prong about 14 inches (35.6 cm) long; two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied. The light box should be mounted at a height such that the top of the third row of letters (0.8 logMAR, 45 letters, 20/125 Snellen) is 49 +/- 2 inches (124.5 +/-5.1 cm) from the floor. The rear of the box provides storage space for the two charts not being used.

Illumination

The overhead room lights should be turned **off** during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect such as glare. With the box light off, not more than 15 foot-candles of light should fall on the center of the chart. The visual acuity light box is equipped with two **20- watt** fluorescent tubes. Because the illumination of fluorescent tubes diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2,000 hours, new tubes should be kept "on" for about 4 days (approximately 96 hours, does not have to be continuous) before use. All tubes should be replaced once a year.

Each tube is partially covered by a 14-inch (35.6 cm) fenestrated sleeve, open in the back, which serves as a baffle to reduce illumination. Each sleeve should be centered on the tube such that an equal length of tube (about 4 and 3/16 inches or 10.6 cm) is left uncovered to the right and left of the sleeve.

4- and 1-Meter Visual Acuity Lanes

A distance of 4 meters (13 feet and 1.5 inches, or 157.5 inches) is required between the subject's eyes and the visual acuity chart for the 4-meter test, and a distance of 1 meter (39 and 3/8 inches) is required for the 1-meter test. The room for visual acuity testing must have, in addition to the 4- meter lane, space for the visual acuity box (and possibly a stand) and space for the subject.

- Wall-mounted box: In addition to the 4-meter lane, 7 inches (17.8 cm) must be allowed for the depth of the box plus space for the subject to sit or stand.
- Stand-mounted box: In addition to the 4-meter lane, 13 inches (33 cm) must be allowed for two of the stand's casters to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the subject to sit or stand.

Marking the Distance

4 Meters

- If the chair and visual acuity box are permanently affixed, distance measurements need to be made only once and no floor marks are needed to ensure the correct distance.
- If the box is mounted on the wall but the subject's chair is not permanently affixed, the 4- meter distance of the subject's eye from the chart must be marked clearly and permanently.

- If the box is mounted on a movable stand, the 4-meter distance must be marked clearly and permanently. The location and orientation of the box must be rechecked each time a new chart is put in place or the box is touched. When the stand touches the rear wall of the room, two of the five casters should touch the wall.

1 Meter

- The 1-meter distance is measured from the eye of the subject, who is seated comfortably in a chair with his or her back firmly placed against the chair's back, to the center of the second (for testing the left eye) or fourth letter (for testing the right eye) of the third line of the chart. A stick, one meter long, should be used to confirm the distance for each subject.

Visual Acuity Procedure

- Visual acuity will be measured at each study visit.
- Visual acuity should be measured for each eye AFTER refraction. Visual acuity should NOT be recorded during the refraction procedure.
- It is very important that the examiner is not aware of the patient's clinical records, in order to minimize bias. Therefore, the visual acuity examiner will not have access to the patient's previous clinical examination or treatment results.
- Visual acuity is tested separately for each eye (one eye at a time). The patient's untested eye will be completely covered with a patch, to block out all light from entering this eye. The examiner must constantly ensure that this eye remains occluded at all times.
- The patient is instructed to read each letter on the chart starting with the largest line, at the 4-meter distance.
- The patient will show the orientation of the tumbling "E" with the hand that they are not using to occlude the untested eye. If the patient cannot identify the orientation of a letter, they are encouraged to guess. **Only one response is allowed per letter**.
- The examiner must ensure that the patient does not squint (creating a pin-hole effect) or lean forward (reducing the distance to the chart).
- Once a patient has given a response for a letter and has moved on to provide a response for the next letter, any corrections of previous response will not be accepted.
- However, if the patient has given a response for a letter and has not yet moved on to provide a response for the next letter, a correction of the previous response is accepted.
- If the subject gives two possible responses for a letter, tell the patient to commit to one answer. **The examiner CANNOT, at any time, give the patient any indication as to whether a response is correct or incorrect.**
- If 3 or fewer letters are identified correctly on any row from Row 3 or below, STOP testing on that row.
- In the case that the patient reads less than 10 letters at 4 meters, move the patient or the chart so that there is a distance between the two of 1 meter.
- Visual acuity will then be retested at this 1 meter distance.
- Only the first 6 rows of letters need to be read at 1 meter.
- If less than 10 letters are read at 1 meter, then the examiner must proceed to Low Vision Testing, starting with Count Fingers testing. If the patient does not adequately Count Fingers (see below), proceed to Hand Motion. If the patient does not adequately recognize Hand Motion (see below), then proceed to Light

Perception.

Testing of Count Fingers Vision

In testing for count fingers vision, the examiner's hand presenting 1, 2, or 5 fingers is held steady at a distance of 1 meter directly in front of the eye being examined. The fellow eye is completely occluded with a patch. Refractive correction should not be used. A light should be shown directly on the hand from behind the subject and room lights should be turned on. The examiner's fingers should be presented in random order and repeated 5 times. Eccentric viewing should be encouraged. If the subject correctly identifies three of the five presentations, then count fingers visions is noted. If not, then the subject must be tested for hand motion vision.

Testing of Hand Motion Vision

The examiner's hand with all fingers spread out should be extended ½ meter directly in front of the eye being examined. The fellow eye should be occluded with a patch. Refractive correction should not be used. A light should be shone directly on the hand from behind the subject and room lights should be turned on. The examiner's hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per second. The subject is instructed that the examiner's hand will be presented and they will have to respond to the question: "What am I doing with my hand?" This should be repeated five times. Four out of five correct responses indicate that hand motions visions is present. If the subject does not correctly identify four out of five, then you must test for light perception.

Testing for Light Perception

The indirect ophthalmoscope is used as the light source for testing light perception. Room lights should be off. The opposite eye must be completely patched. No correction should be used. From a distance of ½ meter with the light source turned up to maximum intensity, the light from the indirect ophthalmoscope is directed into the subject's eye four times. The subject is asked to respond when the light is "on". Light Perception is recorded if the examiner is convinced the subject sees the light. Otherwise, the vision should be recorded as "No Light Perception".

Scoring Best Corrected Visual Acuity

On the Visual Acuity Forms, the examiner will circle all letters read correctly. Letters read incorrectly or not read at all will be left unmarked. At the end of each row of letters, the examiner will write down the total number of letters read correctly on the line provided. If visual acuity was not tested at 1 meter, the examiner will indicate this on the form.

After each measurement of visual acuity, the biostatistician will calculate the score for the visit. The visual acuity score is defined as follows:

- If 10 or more letters of the first line are read correctly at 4 meters, the 4 meter visual acuity score is equal to the number of letters read correctly at 4 meters plus 30.
- If 3 or fewer letters of the largest line are read correctly at 4 meters, the visual acuity score is equal to the number of letters read correctly at 1 meter.
- If 3 or fewer letters are read at 1 meter, then low vision testing must be

performed. (This result, count fingers, hand motion, light perception, or no light perception, will be used for the analysis by converting into a logMAR score according to Visual Acuity Calculation Table).

The highest attainable 4-meter visual acuity score is 100.

The Snellen equivalent, defined as the Snellen ratio corresponding to the most difficult line for which the subject read at least 4 of 5 letters correctly, will also be entered by the examiner on the 4-meter Visual Acuity Form (Section A.5).
The data entry staff will enter the number correct on each row at 4 meters, and if applicable, 1 meter and low vision testing results (They will not enter which letters the examiner circled, i.e., which letters the patient identified correctly.). Coordinating center personnel will double check the data entered by the examiner and data entry staff.

5.2.3.B Visual acuity training and certification

The goal of the certification process is to standardize methodology for refraction and visual acuity measurement. All visual function examinations must be performed by study-certified technicians. The principal investigator at each site is responsible for ensuring that the appropriate personnel are identified, trained and certified. A qualified visual function examiner (SL) from the Clinical Coordinating Center [redacted] will certify the rooms and technicians at each site.

Technicians are expected to perform the refraction and visual acuity tests on at least one and possibly more non-study subjects according to protocol requirements. The examiner will determine whether or not the candidate executes the study protocol accurately for each procedure. A checklist (Visual Acuity/Refraction Certification Form, Section B.1) containing required procedures will be used to facilitate this process.

Room certification will be performed and recorded (Room Certification Form, section B.2) to ensure that all study rooms meet illumination, equipment, and distance requirements. Logs should be kept to document dates of light box bulb replacement.

Certification is valid for a period 18 months (± 2 months) from the date of certification. The process should begin as soon as possible, as technicians must be certified before the first study subject is seen. **A minimum of two certified technicians** are required at each site. The visual acuity measurement schedule may be found on the Study Forms Completion Schedule.

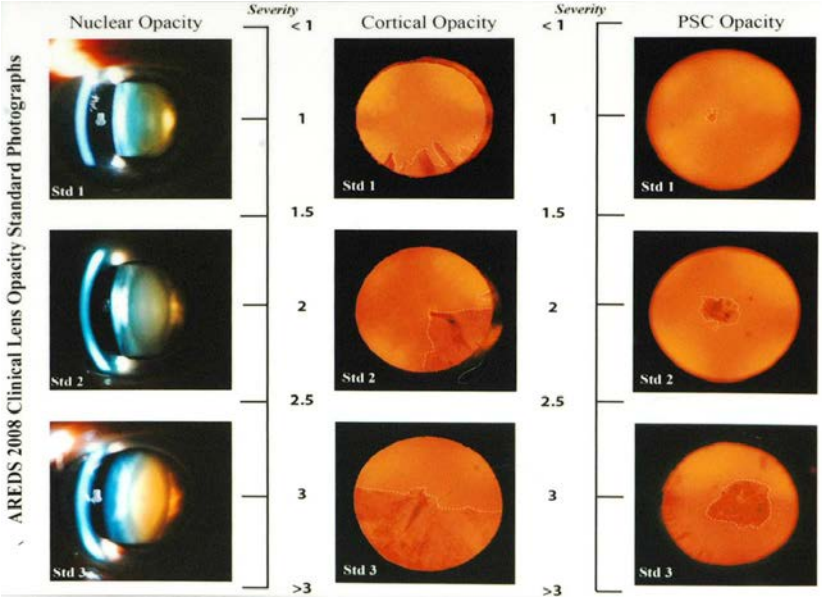
5.3. Ophthalmic procedures

5.3.1. Grading Cataracts

The study ophthalmologist will grade cataracts at every clinical exam based on the Age-Related Eye Disease Study (AREDS) clinical lens grading system (Chew et al., 2010). Pupils must be dilated maximally and lenses should be examined at the slit lamp for the presence and severity of three types of opacity: nuclear, cortical and posterior subcapsular. For each type of opacity, the examiner should compare the lens being examined with the AREDS 2008 Clinical lens opacity standard photographs, of increasing severity. In each series, “1” indicates clinical presence, “2” indicates clinical significance, and “3” indicates severe occurrence. Half grades may be given, for example if a nuclear opacity was thought to be half way between the first and second standard photographs, a decimalized grade of “1.5” could be assigned.

The study ophthalmologists will refer to laminated photos of the scale in real time when making the clinical assessment. If no cataract is present, he/she will indicate this on the clinical exam form.

The following categories of severity are present for all types of opacity (nuclear, cortical and posterior subcapsular): <1, 1, 1.5, 2, 2.5, >3.



*Clinical grading adapted from: Chew EY, KIM J, Sperduto RD et al. Evaluation of the Age-Related Eye Disease Study Clinical Lens Grading System AREDS Report No. 31. Ophthalmology 2010: 11; 2112-2119.

5.3.2. Grading inflammation

Slit lamp examination and dilated funduscopic exam are important parts of our study: assessments of anterior chamber cells and vitreous haze will determine the patient's course of treatment. All of our study physicians are fellowship-trained uveitis specialists who have participated in prior uveitis studies.

The study ophthalmologist at each site will be required to perform an eye examination at each study visit. This examination should be similar to that performed in the routine care of uveitis patients. Several components will be assessed in detail per study protocol. The grading schemes to be used for these assessments are adapted from the Standardization of Uveitis Nomenclature (SUN) Working Group.[2]

Anterior Chamber Cells

SUN Working Group Grading Scheme for Anterior Chamber Cells

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

*Field size is a 1mm by 1mm slit lamp beam. Grading should be done with the highest magnification and illumination and conducted in a completely dark room, prior to dilation.

Anterior Chamber Flare

Anterior Chamber Flare will be assessed by slit lamp exam but will not be part of our study criteria for controlled inflammation.

SUN Working Group Grading Scheme for Anterior Chamber Flare

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

*Adapted from: Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis: I. Anterior Uveitis. AM J Ophthal 1964;47:155-170; Grading should be conducted in a completely dark room

Vitreous Cells

There is currently no accepted standard for grading vitreous cells, which will not be part of our study criteria for controlled inflammation. However, we will collect this information using the grading scheme below, which is adapted from the [redacted]:

Grade	Cells in Field*
0	No cells
0.5+	0 to 5 cells
1+	6-10 cells
2+	11-20 cells
3+	21-50 cells
4+	>50

*Field size is a 1mm by 0.5mm beam; Grading should be conducted in a completely dark room; These cells are graded by slit lamp exam after dilation.

Vitreous Haze

Vitreous haze will be assessed using an indirect ophthalmoscope set at mid-power and a 20D lens. Fundus examination will be done with the last view being the area around the optic disc. The examiner should then compare this view to the photograph (Figure 1) and determine the level of vitreous haze. The National Eye Institute System for grading vitreous haze will be used for all primary and secondary outcome measures. Additionally, vitreous haze will be assessed separately on the 9-point grading scale recently published by Davis et al., known as the Miami scale. The examiner should compare the vitreous haze view with the Miami photograph. An exploratory analysis will correlate measurements from the NEI and Miami scales. Clinical measurements of vitreous haze will also be compared to objective assessments done by grading of fundus photos by the reading center.

If the physician thinks that the grading of vitreous haze is affected by a significant media opacity (i.e. a dense/mature cataract) they should indicate on the Clinical Exam Form that they cannot make a reliable judgment of vitreous haze due to the opacity.

Figure 1: National Eye Institute system for grading vitreous haze

Grade	Description
0	Clear
0.5+	Slight blurring of optic disc margin Normal striations and reflex of nerve fiber layer cannot be visualized
1+	Opacities without obscuration of retinal details
2+	Few opacities resulting in mild blurring of details of optic nerve and retinal vessels
3+	Optic nerve head and retinal vessels significantly blurred but still visible
4+	Dense opacity obscuring optic nerve head

*Grading should be conducted in a completely dark room; From Nussenblatt et al.Standardization of vitreal inflammatory activity in intermediate and posterior uveitis.Ophthalmology1985;92:467-471.

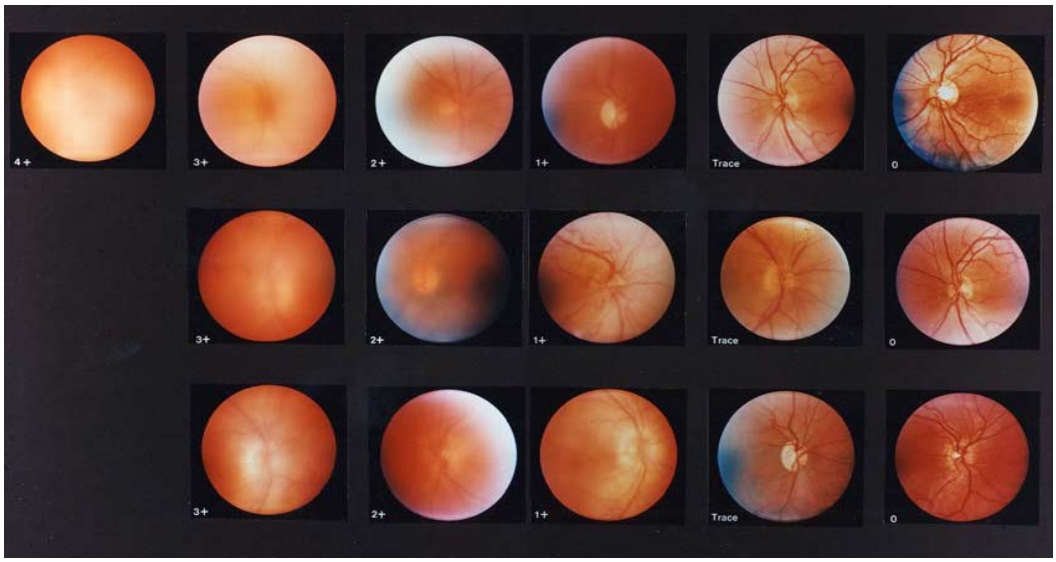
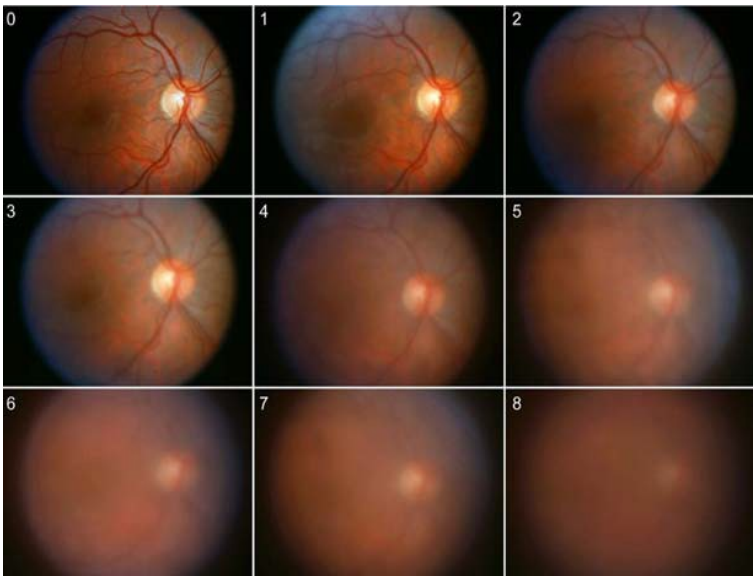


Figure 2: Miami 9-point system for grading vitreous haze



Miami Scale for photographic grading of vitreous haze in uveitis. Am J Ophth;150:637-641 e1.

Grading Retinal/Choroidal Inflammation

Assessment of active inflammation of the retina and choroid should be based on the clinical exam and ancillary testing if needed for certain diseases (i.e. fluorescein angiogram, fundus photography, B-scan ultrasound). Please refer to the table in Appendix F for imaging required for assessing uveitis activity by disease.
Active vasculitis posterior to the equator qualifies as active inflammation, but according to SUN criteria should be confirmed with a fluorescein angiogram. Macular edema in isolation is not sufficient to qualify as active inflammation, but a bullous serous retinal detachment, with any amount of accompanying vitreous, retinal or choroidal inflammation would qualify as an active inflammation. In addition, per protocol, if patients have ≥1+ anterior chamber inflammation, vitreous haze and/or other retinal/choroidal lesions aside from macular edema, that would qualify as active as well.

5.3.3. Inter-observer variation of ocular inflammation

At Baseline (Phase I and Phase II) the 6th month study visit (Phase I and Phase II), the 12th month study visit (Phase I), or at treatment failure (whichever is earlier), inter-observer agreement on slit lamp observations and funduscopic exam will be assessed. Coordinators will arrange for two certified study physicians to measure anterior chamber cells, anterior chamber flare, vitreous cells, vitreous haze, and retinal/choroidal lesions at the Month 6 and 12 visit or at declaration of treatment failure. The inter- observer variation will be reported. The primary study ophthalmologist's measurements will be used for primary analysis.

5.3.4. Training and certification of ophthalmologists and study coordinators

All exams must be performed by uveitis specialists. The study protocol and classification system for grading inflammation will be reviewed by [redacted] (or another study ophthalmologist from [redacted]) with the investigators at all sites. An open-book exam on the study protocol will be administered, and a score of 80% is needed for

certification to participate in the trial. For investigators with scores less than 80%, additional instruction and a re-test will be done. Prior to study start, each site investigator will grade inflammation on 5 uveitis patients and scores will be compared to the [redacted] investigator's scores. If a discrepancy of greater than 1 grade in any of the measurements occurs, then additional patients will be graded until there are 5 consecutive patients where the grade is within 1 level for each of the measurements (i.e. anterior chamber cells, vitreous haze, and retinal/choroidal lesions). If both graders assess each area to have 0 inflammation in a particular patient, that patient would not count towards the 5 patients needed to complete the training. This grading assessment will be done prior to initiation of the trial and yearly thereafter. Duplicate measurements of inflammation will also be collected at the 6 and/or 12-month study visits. Inter-observer agreement will be reported.

The study protocol will be reviewed with all study coordinators by coordinating center personnel. An open-book exam on the study protocol will be administered, and a score of 80% is needed for certification to participate in the trial. For coordinators with scores less than 80%, additional instruction and a re-test will be done.

5.4. Optical coherence tomography

We will be using spectral-domain optical coherence tomography (SD-OCT) in this study to monitor the effects of treatment by measuring macular thickness and changes in macular thickness. We will be utilizing the Heidelberg Spectralis SD-OCT unit for all study assessments. Each site must have access to the Heidelberg Spectralis unit at the time of study initiation and must continue to use that same scanner for all patients for the duration of the study. If Heidelberg Spectralis is not available, the Zeiss Cirrus SD-OCT may be used.

5.4.1. Required patient assessments—Heidelberg Spectralis

For our study, one of each of the following scans is required for each eye:

- **20° x 20° High Speed Volume scan centered on the macula**
    - 20° x 20°
    - 49 sections
    - 16 frames (ART)
- **7-Lines scan centered on the macula**
    - 30° x 5°
    - 7 sections
    - 25 frames (ART)

5.4.2. Scan procedures—Heidelberg Spectralis

Procedures for Obtaining Scans

General Guidelines

- Scans may be obtained if the patient's pupils are not dilated. However, pupil dilation prior to obtaining scans is encouraged
- Clean chin rest and forehead rests
- Adjust table and chin rest height to ensure patient comfort
- Make sure that patient is aligned straight; slight face turns to the left or right may decrease scan quality

Click on the Preset **"Dense"** scan icon on the screen to obtain the 20° x 20° volume scan. Please make sure that the scan will have the following parameters:

- 20° x 20°
- 49 sections
- 16 frames (ART)

- Pull the camera all the way back
- Move the instrument toward the patient slowly, taking care not to alarm patient and to not touch the patient's eyes or eyelashes with the instrument
- Ask patient to fixate on the blue light on the inside of the machine
- Remind patient not to follow the movement of the red scan lines
- If patient is having trouble focusing on fixation light, you may need to help the patient direct his/her gaze by using external fixation targets
- Focus in on the circular black and white retinal reflex
- Move the camera forward so that the fundus image comes into view and fills the screen
- Use the focusing knob to obtain maximum brightness and clarity of the image
- Ensure that the image is maintained in the **upper third** of the screen
- Click "Acquire"
- Repeat for next eye

Click on the "**7 Lines"** Preset Scan icon
This scan will have the following parameters:

- 30° x 5°
- 7 sections
- 25 frames (ART)

- Focus image as described above
- Click "Acquire"
- Repeat for next eye
- **Please review scans for completeness and quality. A good quality scan should have a score of at least 20. Please repeat any scans that are not complete or of poor quality.**

5.4.3. Obtaining retinal thickness data—Heidelberg Spectralis

- After closing the acquisition window, double click on the volume scan.
- Select "Thickness Map" tab
- Record central subfield thickness of each eye on data sheet
- Print out copy of scan for patient file

Be sure to complete analysis of data and record information on data collection form as soon as possible. This will ensure that the treating physician will be able to use the SD-OCT results in real time to determine if macular edema is present or not.

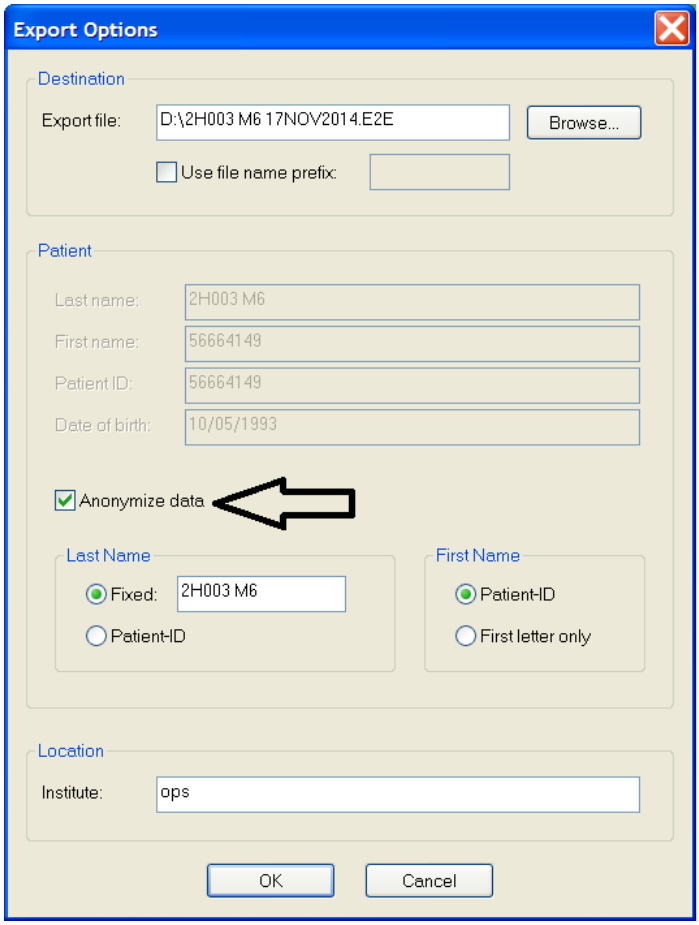
5.4.4. Saving/Exporting data—Heidelberg Spectralis

Saving Data

- All scans should be saved and archived at each study site on the Heidleberg SD-OCT unit.
- Even if your clinic saves all scans onto a server, please follow the instructions

below to save all scans for FAST study patients onto an external hard drive.

- After obtaining scans, highlight all study scans together, right click and choose “Export as E2E”
- Click on the “Anonymize data” box in order to ensure patient confidentiality
- In the “Export File” filed: Name the E2E file as “Patient Study ID-Visit Number-Date of visit”, example “2H003-M6-17NOV2014”
- In the “Last Name” field: Type in the Patient’s Study ID and Visit, example “2H003 M6”



- Save the “E2E” data onto a removable hard drive separate from the main unit; this raw data may be requested from each site at a later date.
- Please ensure that your removable storage drive(s) is/are HIPAA compliant as defined by your institution

Exporting E2E Data to Reading Center

- Create a folder on the desktop and/or on a removable drive for each patient visit: Label this new folder with “Study-SiteID-Patient Study ID-Visit Number- Date of visit”, example: “FAST-[redacted]-2Q001-M1-10AUG2012”
- Place the E2E file into the folder
- Complete a “FAST Study Transmittal Form” (electronic copy or scan completed paper form) and add into the created folder
  - In the “Clinic ID” field of the Transmittal Form, please enter the 4-letter code for your clinic. Contact coordinating center if you have any questions regarding your Clinic ID code.

- If images cannot be obtained or are of poor quality, please provide comments on the Transmittal Form

- Compress the folder into "ZIP" format.
- Upload the ZIP folder to the Uveitis Reading Center server:

[redacted]

5.4.5. Required patient assessments—Zeiss Cirrus

For our study, one of each of the following scans is required for each eye:

- **Macular Cube Scan**
- **5 Line Raster scan centered on the macula**

5.4.6. Scan procedures—Zeiss Cirrus

Creating Patient Files

To ensure patient confidentiality, patient ID only will be used. Patient name and other identifying information will not be used on the scans. Therefore, when setting up the patient file, please follow the instructions below:

- In the Last Name field, enter study name: FAST
- In the First Name field, enter patient's unique study number
- For Date of Birth, always use 1/1/2000
- Click proper field in gender section
- In Patient ID field enter patient's unique study ID number, example: "1Q001"

Procedures for Obtaining Scans

General Guidelines

- Scans may be obtained if the patient's pupils are not dilated. However, pupil dilation prior to obtaining scans is encouraged
- Clean chin rest and forehead rests
- Adjust table and chin rest height to ensure patient comfort
- Make sure that patient is aligned straight; slight face turns to the left or right may decrease scan quality
- Ensure that the camera is pulled all the way back
- Move the instrument toward the patient slowly, taking care not to alarm patient and to not touch the patient's eyes or eyelashes with the instrument

Select **"Scan Macular Cube 512x218 HD"** default in the upper panel of the Acquire screen

- In the Iris Viewport, center the scan beam through the pupil by clicking on the pupil center or using the X-Y controls
- Focus the iris image using the chinrest arrows
- Center the fundus image in the Fundus Viewport
- Click on "Auto Focus"
- Use small arrows to focus manually
- Click "Optimize"
- Ask patient to blink right before image capture
- Click "Capture"
- Review scan; if acceptable, click "Save"

- If not acceptable, click "Try Again"

Repeat above steps to acquire **"5 Line Raster HD"** default Scan

- If patient is having trouble focusing on fixation light, you may need to help the patient direct his/her gaze by using external fixation targets
- Ensure that the scan image is maintained in the **upper half** of the screen
- Please review scans for completeness and quality. Signal strength should be at least 5 or higher. Please repeat any scans that are not complete or of poor quality.

5.4.7. Obtaining retinal thickness data—Zeiss Cirrus

- Obtain Macular Thickness analysis
- Obtain 5 Line Raster analysis
- Record central subfield thickness on data sheet

Be sure to complete analysis of data and record information on data collection form as soon as possible. This will ensure that the treating physician will be able to use the SD-OCT results in real time to determine if macular edema is present or not.

5.4.8. Saving/Exporting data—Zeiss Cirrus

- All scans should be saved and archived at each study site on the Zeiss Cirrus SD-OCT unit. This raw data should also be saved onto a separate removable hard drive so that it is available for export and review at a later date.
- The following images should be uploaded to the server of the Uveitis Reading Center for review.
  - Under *Records* select *Export Exams*
  - Browse to folder where to save files
  - Search for the subject to export
  - Under *Exam Export* select the *Eye(s)* and *Exam Type* for the visit you want to export
  - Select *Export*
  - Label the file with patient's unique study ID, visit number, and date of visit, example: "FAST_1Q001_BL_10AUG2012_IB"
  - Fill out transmittal form
  - Compress the folder containing the image files for both eyes and the Transmittal form in ZIP format
- Upload the ZIP folder to the Uveitis Reading Center server:

[redacted]

5.4.9. OCT operator qualifications

Prior to the study start date, at least 2 personnel who will be responsible for obtaining SD-OCT scans at each site should be identified. These individuals should have prior experience with operation of either the Heidelberg SD-OCT or Zeiss Cirrus SD-OCT instrument for routine clinic purposes. Personnel from the coordinating center will go to each

site before that start of the trial to meet with these technicians to review all required OCT procedures specified in our protocol. OCT operators must be able to demonstrate ability to obtain quality scans as well as knowledge of the study protocol.

5.5. Fundus Photography

Color fundus photography will be performed at baseline, 6 months, 12 months or treatment failure. Photos will include fundus reflex images and non-stereoscopic fundus images. Images should be uploaded to: http://eyehealthusf.org/uploadi/index.php according to instructions in UPRC manual.

Vitreous haze will be graded according to the NEI and Miami scales by masked graders. Photographers will need to be certified by the Uveitis Photograph Reading Center prior to obtaining photos for our study. Please see UPRC manual (Appendix E) for instructions on certification and obtaining study photos.

5.6. Laboratory measurements

Hematology and serum chemistry will be monitored in all patients prior to enrollment and throughout participation in the study. Each of the participating sites has an accredited onsite laboratory where all blood draws and laboratory measurements will be performed. The following will be measured and recorded on the Laboratory Report Form (Section A.8) for each:

Hematology
- Hemoglobin and/or hematocrit
- Platelet count
- White blood cell count (WBC)
  - % neutrophils; % lymphocytes
  - CD4 lymphocyte count ([redacted] *sites only, at Baseline, Month 3, 6, & 12*)

Serum Chemistry
- SGOT (AST)
- SGPT (ALT)
- Creatinine
- Serum or urine pregnancy test

Laboratory measurements used for baseline visits should be collected 4 weeks prior to enrollment. Those used for follow-up visits may be collected at any time within the study visit window. Laboratory measurements must be collected at each study visit.

All abnormal values will be reported on the Adverse Event Checklist (Section A.10) and monitored for resolution on the Adverse Event Log. Abnormalities which result in a non-serious adverse event (i.e. AST or ALT increasing to twice the upper limit of normal) will result in immediate stopping of study medications. As these abnormalities are often reversible, patients will be allowed one month to regain eligibility. If the lab results have returned to normal within one month, patients may be re-administered the study drug according to protocol. Labs can be checked prior to one month, and if normal, treatment can resume. Otherwise, treatment failure will be declared and patients may be treated according to best medical judgment of physician. They should still be followed for their 6th months visit and be treated according to the best medical judgment of their physician.

Laboratory abnormalities which meet the designated threshold of a severe adverse event (SAE) will result in immediate stopping of study medications, and should be reported on the Serious Adverse Event Narrative form (Section A.12). Treatment failure will be declared, and patients will be treated according to the best medical judgment of their physician, but still follow-up for 6 months. If a lab SAE occurs, patients will not switch to Phase II.

6. Adverse events

6.1. Non-serious adverse event (AE) *see the adverse event checklist (Section A.10)

Non-serious adverse events may include any unfavorable medical occurrences in patients who have ever received study medication, regardless of any causal relationship with treatment. Examples may include*:

- Increased intraocular pressure (>24 mm Hg)
- Abnormal lab findings (≥ 2 times but < 5 times the upper limit of normal AST or ALT, rise in creatinine to ≥ 1.5 to < 2 mg/dL, reduction of white blood cell count to below 2.5)
- Concurrent accident or illness
- Increase in the frequency and severity of symptoms of a pre-existing condition
- Side effects such as gastrointestinal upset, nausea, vomiting, fatigue

6.2. Serious adverse event (SAE) *see the adverse event checklist (Section A.10)

Serious adverse events include any medical occurrence that results in the following outcomes, or any other adverse event classified as severe*:

- ≥ 5 times the upper limit of normal AST or ALT
- Death
- Non-elective surgery or hospitalization for any reason
- Myocardial infarction or stroke
- Life-threatening adverse drug experience or any life threatening event
- Persistent or significant disability or incapacity
- Cancer
- Seizure
- Congenital anomaly/birth defect
- Disability or permanent damage
- Required intervention to prevent permanent impairment/damage

6.3. Adverse event reporting

Non-serious and serious adverse events will be recorded at each study visit on the appropriate form (Adverse Event Checklist and Log, Sections A.10-A.11). An adverse event log will be maintained for each patient to record the onset and resolution of any adverse events. The Adverse Event Checklist will initially be completed by the study coordinator while meeting with the patient at the beginning of each study visit. If there are any reported symptoms (not only severe symptoms), the study physician will review them with the patient while remaining masked to determine if any action is needed.

In case of a Serious Adverse Event (SAE), the Serious Adverse Event Narrative Form (Section A.12) will be completed by the Investigator and submitted to the Medical Monitor, [redacted] Principal Investigator [redacted] and the Coordinating Center Manager [redacted] **within 24 hours** of the SAE. Information recorded on this form will include the nature of the

event, date of onset, date of resolution, date of notification to Medical Monitor, and action taken. The Medical Monitor will review, sign, decide if the serious adverse event was related to the study drug, and collect additional information if needed.

If any serious adverse event other than a laboratory abnormality occurs, treatment failure cannot be declared until the Medical Monitor judges that the SAE is related to the study drug. This will require the investigator notifying the Medical Monitor about the event, and the Medical Monitor contacting the investigator regarding his determination. The Medical Monitor will determine two things: 1) whether this is a true treatment failure because the SAE is likely related to the study drug, and 2) whether it is safe to switch the patient to Phase II. If it is not safe to switch the patient will be treated with best medical judgment and still be followed for 6 months.

If the investigator thinks the SAE is related to the study drug, he/she can stop the study medication anytime (including prior to determination of treatment failure by the medical monitor). If the investigator thinks treatment failure is likely (prior to hearing from the Medical Monitor) they should obtain all study assessments, which would be collected at a treatment failure visit. However, the investigator will wait to complete the Treatment Assessment Form and officially declare treatment failure, until they are instructed to do so by the Medical Monitor.

Any significant study drug-related adverse events will be reported by the coordinating center to the FDA and CHR office as appropriate. The principal statistician will inform the DSMC of serious adverse events by arm every six months.

6.4. Patient death

Any patient death that occurs during the study will be reported by the study center's Study Coordinator to the Medical Monitor within 24 hours. The study arm of any deceased patient will be made available to the DSMC by the DCC if appropriate.

7. Data collection and management

This section discusses how the data will be collected from the different Study Centers, entered into the computer database and stored, and transferred to the Data Analysis Committee under the supervision of the Data Coordinating Center (DCC). The data management plan described below is similar to what we are already using for [redacted] is the clinical and data coordinating center for these trials.

7.1. Data collection forms

The data collection forms are derived from the [redacted] These forms have been extensively field-tested by [redacted] investigators.

Study personnel at each site will be given specific training for each form for which they will be responsible. Paper forms for each patient will be completed by study personnel (study physicians, refractionists, etc.) on paper in real time when the patient is being

assessed. Teleconferences and site visits will be held periodically for all users of the forms to review procedures and address questions.

7.2. Data review

Data will be reviewed in real time, as the patient is being assessed. The study coordinator will verify with the personnel filling out the forms that they are complete. Before scanning to be sent to [redacted] for data entry, the forms will be reviewed and cross-checked for consistency and completeness by the study coordinator within **24 hours** of completing the form. If the forms are not filled out completely, the study coordinator will contact the person responsible for completing the form to provide the missing data, or clarify any inconsistent data. The study coordinator or investigators who filled out the form are the only people who are authorized to add missing data or make any changes to the study forms. All changes should be made with a red ink pen, and then signed and dated. Further investigation may be conducted if certain fields or personnel are associated with a higher rate of paper form errors.

7.3. Data entry

Once the completed study forms have been reviewed and approved by the study coordinator, the study coordinator will scan and email the forms to the study email address ([redacted]) **within 10 days** of the patient visit. All data will be entered into the official electronic research data capture service at [redacted]: REDCap. Each study form will be double entered by two independent data entry operators at [redacted] The data entry manager will merge the entries, checking for any inconsistencies or errors. The goal is for both data entries and data merging to occur within 10 days of receiving the completed forms in order to prevent the accumulation of un-entered forms. The database program contains an entry module for each form, prompting the user to enter the data in the same order as the form and clearly indicating each question.

7.3.1. Data entry errors

The data entry manager will compare double-entered study data using the automated feature in REDCap. Wherever there is a mismatch, an error file will be generated with relevant data such as the form, field name, visit name, and data for which discrepancy is found. The data entry manager will then contact the data entry operators to verify the forms and re-enter the data. Discrepancies and missing values will be assessed by the data entry manager, and resolved by queries sent to the study coordinator and appropriate observers (clinician, refractionist, etc). A logfile will preserve the date and time of any changes, together with who entered the changes.

7.3.2. Data consistency and validity

A database data quality assessment program will be created in R programming software to help prevent inconsistencies or invalid data. The database program will check for the following errors: (1) improper entry of the patient ID based on the checksum, (2) data fields that are out of range, (3) inconsistent or illogical entries, (4) incompleteness, and (5) numerical values that are far outside the range of those previously entered. The software will create an error file with relevant data such as the form identification, field names and the data. Automated checks will be made to ensure consistency and that each variable in the analysis set has in-range values (protecting against negative ages, spelling errors in

categorical factors, and similar errors). The DCC will conduct regular checks of the data at each site and will contact the study coordinator about any errors in order to resolve the inconsistencies and have the data entry operators enter the correct data.

7.3.3. Data preparation and cleaning

Data sets for analysis will be produced in Microsoft Excel® worksheets (downloaded from the REDCap system) containing a single header line whose variable names match the REDCap database. Each analysis set will be in the form of a rectangular table in which each column corresponds to a single variable and each row to an observation. All missing values will be coded explicitly using the string "NA" (as used in the R software). Codes for categorical variables (such as 1 for male, and 2 for female) will be avoided in favor of self-documenting character strings (such as Male, Female) whenever possible.

A detailed codebook will be prepared, containing for each variable, (a) the form from which the variable derived, (b) the text of the question, (c) all possible values for the variable, and (d) summary statistics for the variable. Note that all codes and character strings that represent categorical factors will be clearly defined in the codebook. Units for each continuous variable (e.g. logMAR) will be unambiguously indicated for each variable. Each release of the analysis set will be accompanied by the corresponding version of the codebook. Version numbering with dates will be strictly observed.

7.3.4. Monitoring

We will maintain a record of (1) changes to the initial entries on database forms, and (2) changes made to all entered data. Database errors include (a) missing information, (b) erroneous information that was initially entered, and (c) errors arising from difficulties with the forms themselves. Quality assurance reports will summarize the number of each of these. Most importantly, we will closely monitor the waiting time between the collection of the initial form and the entry of the data. If entry times exceed 30 days, then this will trigger a response, which may include investigation, retraining, and even reassignment.

7.4. Data analysis

Following data checks by the data analyst, the Data Analysis Committee will be responsible for analyzing the data. At designated time points, it will be merged the unmasked data with the randomization list, perform statistical analyses and prepare reports.

Standard report-generation software included with the R statistical and data analysis package will be used to ensure consistency of the codebook and analysis set at all times.

Data monitoring reports will be prepared based on analysis data sets. These will be prepared using report-generation software. Monitoring reports will include (a) recruitment reports for each center, (b) compliance reports, (c) retention reports, and (d) data quality reports. These will be reviewed by the DCC on a monthly basis, and communicated to the study sites on a monthly basis.

7.5. Data storage and security

Paper forms will be maintained in locked file cabinets in locked rooms only accessible to research staff at each study site. All PDFs of forms will be sent to the study coordinator at

[redacted] They should be sent through a secure email and saved on a secure server.

All electronic storage will be subject to standard security procedures in compliance with established enterprise information security standards. Each computer will be hardware-firewalled and will not be accessible outside the Local Area Network. Hard-disk encryption will be used for each machine, and the machine will not be accessible without a network account and password. Only one individual at each site will have password access to the machine; new accounts may be provided by the local network administrator only with the approval of the DCC. Accounts will be immediately deactivated for data entry or other personnel who leave the study. The computer used for data entry and storage will be kept in a physically locked room, and only authorized study personnel will be able to access this machine. All individuals who access the server room will be logged as to time and date. At each center, the complete database (including all data tables as well as change logs) will be backed up weekly on the server and weekly on a CD/DVD, which will be kept at a safe, locked cabinet. Temperature logs will be maintained for the server room and reported.

The database at the DCC will be stored on a SQL server located at [redacted] and three sets of backup copies on CD/DVD will be kept. The server is hardware-firewalled and also uses hard-disk encryption; it is inaccessible outside the [redacted] network and cannot be physically accessed by anyone other than the network administrator. Other visitors must be accompanied by an information security professional and the visit will be logged. All data will be protected with passwords and the computer/server on which the data is stored and the backup copies on CD/DVD will be located in a lock-secured facility. Each back-up file will be archived offsite. In the event of disruption due to unforeseen circumstances, all materials needed to continue will be available from the offsite archive.

8. Quality control

With the help of the Data Coordinating Center and the Data Analysis Committee, the Clinical Coordinating Center will evaluate the quality of study activities (clinical examination, treatment compliance, refraction, etc.).

8.1. Medication storage and expiry

Study medications will be stored at room temperature. The expiration dates of the treatment kits will be regularly monitored and all expired study medicine will be discarded appropriately.

8.2. Periodic reports

The Study Coordinators will send weekly reports to the clinical coordinating center, on the number of eligible patients screened, the number of patients enrolled, reasons for ineligibility, and the number of patients who have come back for follow-up visits. This will be used to monitor the enrollment/follow-up progress and any protocol violation in enrollment. The CCC will send monthly reports to all investigators with a summary of overall enrollment and breakdown of enrollment at each site.

When a site visit or training/certification is conducted at a study site, a report will be prepared and sent to the Executive Committee.

The minutes of the DSMC meeting will be circulated electronically among the investigators and the members of the DSMC after each meeting.

8.3. Data management, security and quality assurance

See Section 7.

8.4. Monitoring compliance

Patients will be asked to record missed doses in individual treatment calendars and to bring them with their medication to each follow-up visit. The study coordinator will collect details of the number of doses missed by the patient and record these in the medication log. In addition study coordinators will conduct pill counts at each visit.

8.5. Certification

For training and certification process, see Sections 5.2.3.

8.6. Data audits

Samples of data forms will be audited at each site to ensure consistency between the source documents and data entry. Patient charts will also be reviewed two times a year to confirm adherence to the protocol.

9. Duties and responsibilities of staff

9.1. Ophthalmologist

- Note: whenever possible, the primary study ophthalmologist should be the same person across all a patient's study visits, for consistency of measurements
- Responsible for enrolling study subjects
- Provide information for completing the clinical examination forms
- Obtain written consent from the subjects with the help of study coordinator
- Initiate study medication as per the randomization
- Responsible for the care of the patient throughout the course of the study
- Manage adverse events

9.2. Clinical Trial Manager

- Ensure the execution of the study as per the protocol
- Arrange training of the ophthalmic assistants, and refractionists
- Coordinate with the collaborating centers
- Prepare monthly reports regarding recruitment and follow-up progress
- Handle correspondence between centers
- Maintain IRB approval and renewals
- Communicate with central pharmacy regarding drug orders and distribution to sites

9.3. Study Coordinator

- Make sure that appropriate patients are screened and enrolled in to the study (including obtaining appropriate assent/consent)
- Prepare weekly reports regarding recruitment and follow-up progress
- Send reminders to study patients for follow-up visits
- Meet with the patient at each study visit, prior to the study ophthalmologist to help maintain masking

- Assist ophthalmologist, ophthalmic assistants, and refractionists with conforming to study procedures
- Verify data forms for completion and collect missing information
- Send study forms for prompt data entry
- Maintain stock of and dispense study medications

9.4. Data Analyst

- Develop data entry programs specific to the study forms under the supervision of DCC
- Monitor the flow of forms from the coordinator
- Supervise data entry operators for any errors or omissions
- Develop consistency checks
- Communicate with study coordinators and data entry operators to correct any mistakes in study forms and data entry
- Transfer data as and when requested by the DCC
- Back up all data appropriately

9.5. Data Entry Operator

- Enter all data from study forms when submitted by the study coordinator
- Verify inconsistencies in the forms and send them for correction to the study coordinator
- Perform double entry to ensure accurate recording

9.6. Biostatistician [redacted]

- Review data for quality control purposes
- Prepare reports for DSMC
- Lock database at completion of study after database is cleaned
- Conduct analyses at the conclusion of the study
- Prepare randomization list and distribute the list to a pharmacist and non-masked, senior physicians at the study sites in case of emergency.

9.7. Ophthalmic Assistants

- Obtain patient information
- Measure preliminary vision
- Assist ophthalmologist in the clinical examination/enrollment of the subject
- Counsel and motivate patients to return for scheduled follow-up visits

9.8. Refractionists

- Perform manifest refraction as specified by protocol of both eyes at each visit
- Measure and record best spectacle-corrected visual acuity at each visit
- Enter visual acuity (number of letters read and Snellen equivalent) on the form

9.9. OCT Operators

- Perform OCT photography as specified by protocol of both eyes at all visits

9.10. Fundus Photographers

- Perform fundus photography as specified by protocol of both eyes at the baseline, 6 months, 12 months or treatment failure visits

9.11. The Reading Center

- Complete grading of vitreous haze from images of fundus photography
- Process OCT images

10. Study Organization

10.1. Executive Committee

The Executive Committee will be chaired by [redacted] and will include [redacted]. This committee will act as the administrative and executive arm of the clinical trial and will meet once a month to provide overall oversight for the study and make decisions on day-to-day operational issues. The role of the Executive Committee includes monitoring study progress and data collection process, supervising the Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC) for overall quality control, evaluating and adopting changes in study procedures as necessary, communicating with and implementing recommendations from the Data and Safety Monitoring Committee, making executive decisions on the allocation of resources, establishing policies on publications and authorship, and approving and overseeing ancillary studies.

10.2. Clinical Coordinating Center (CCC)

[redacted] will also be responsible for directing the CCC, located at the [redacted] The responsibility of the CCC includes oversight and coordination of the clinical implementation of the trial at all sites. Specifically, this includes roles such as maintaining an up-to-date manual of operations, obtaining human research approvals from Institutional Review Boards, conducting training and certification of all personnel including physicians and refractionists, supervising preparation and dispensing of study medication, ensuring proper masking, and monitoring protocol adherence and recruitment. The CCC will monitor the recruitment progress with weekly reports from each of the study sites. It will also organize twice yearly site visits to conduct chart reviews, training and certification of study personnel and monthly phone calls with study investigators to review enrollment, retention and any other study-related issues. The coordinating center will be responsible for training/certifying study refractionists and managing the refraction protocol. [redacted] will serve as medical monitor of the trial. He will receive all reports of serious adverse events from all study sites, ascertain whether further information is needed, and convey that information to the DSMC. As with our current NEI-funded studies, the study coordinator at [redacted] will serve as the manager of the coordinating center and will assist with many of the clinical coordination activities listed above and also check in weekly by email with the study coordinators at each site to discuss any study-related issues.

10.3. Uveitis Photograph Reading Center (UPRC)

The [redacted], run by [redacted], will receive OCT and fundus photos from all study sites. Grading of OCT and fundus photography will be conducted by trained personnel. They will assess type of macular edema, presence of

epiretinal membrane, and evaluate vitreous haze using the NEI and Miami scale fundus photos. They will also be responsible for monitoring quality of images.

10.4. Data Coordinating Center (DCC)

The DCC including, [redacted], is responsible for supervising data collection, data management, data quality control, data analysis, event adjudication, and training and certification of study site staff in the data management systems. The DCC will also be responsible for coordinating and supporting the activities of the Data Safety Monitoring Committee, including preparing interim and final data reports and organizing meetings with the Data Analysis Committee. The DCC will also be responsible for the dissemination of datasets for use by the Data Analysis Committee and other investigators. The DCC will meet weekly to monitor the progress and quality of data entry/management and address any issues. The DCC will be in close contact with the data analysts and data entry operators to ensure quality assurance of data entry. See MOP for further information on data management (Section 7).

10.5. Data Analysis Center (DAC)

[redacted] will direct the Data Analysis Committee with assistance from the data manager. The primary functions of the DAC include designing a statistical analysis plan, preparing and distributing randomization lists, performing data analysis, and coordinating publications and presentations. The Committee is responsible for obtaining data from the Data Coordinating Center, performing unmasked data analyses and for preparing reports for the Data and Safety Monitoring Committee, and at the conclusion of the study, for the Principal Investigator. The DAC will also be responsible for conducting the prespecified interim analysis (when 1/3rd and 2/3^{rds} of the primary outcome data has been collected) and also for providing data to the DSMC to evaluate the stopping guidelines.

10.6. Data Safety and Monitoring Committee (DSMC)

The Data Safety and Monitoring Committee (DSMC) is independent and NEI-appointed, with experts from diverse fields including ethics, biostatistics, epidemiology, ophthalmology, and international health care, and include at least one member of the NEI staff as an ex officio member. The committee will meet for the first time before the study begins. Only after the DSMC reviews and approves the protocol will patients be enrolled. We anticipate the group will meet regularly throughout the study and review information on data quality, enrollment, patient retention, and study outcomes, etc. Committee members will be unmasked and receive reports of the data with ARM information at two interim time-points (when 1/3rd and 2/3^{rds} of the primary outcome has been collected). They will also receive reports of serious adverse events from the principal statistician, every 6 months.

10.7. Editorial Committee

The Editorial Committee is composed of the principal investigator [redacted] and co-investigators [redacted] This committee has the responsibility to assist in the preparation of the primary study results and to review secondary manuscripts produced by the study investigators. They have the responsibility to ensure the completion of the primary manuscript (Specific Aim 1) in a timely manner and direct its submission for publication.

10.8. Study Sites

Under the supervision of the CCC, [redacted] will direct the Indian centers, [redacted] will direct the Oregon center, [redacted] will direct the Mexico City center, [redacted] will direct the Melbourne center, [redacted] will direct the Chicago center, [redacted] will direct the Riyadh center, and [redacted] will direct the San Francisco center.

10.9. Pharmacy

The [redacted] can handle high volume orders and provide quick turn-around timesto ensure a steady supply of medications over the course of the trial. They have participated in a number of clinical trials and will be able to package and bottle the drugs to fit the specifications of the study protocol. The [redacted] will prepare all of the study medications for the trial.

10.10 Study Communications

The study coordinator at the [redacted] will be responsible for ensuring that communication between all facilities and committees is conducted seamlessly. Communication between study personnel at the [redacted] and investigators at other sites will be performed by extensive use of secure email. Much of the communication will be through email, but we have found that regular, international, conference calls are valuable and that regular, face-to-face meetings are mandatory. Members of the CCC and the DCC at the [redacted] will visit sites every 4-6 months through the duration of the study to discuss details of the study and monitor quality control.

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FAST Uveitis Trial

Statistical Analysis Plan

Confidential

Version 1.5, March 9, 2017

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FI Proctor Foundation Data
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1 Introduction

This document (Statistical Analysis Plan, SAP) describes the planned analysis and reporting for **the FAST (First-line Antimetabolites as Steroid-Sparing Treatment) Uveitis Trial**, University of California, San Francisco. It includes specifications for the statistical analyses and tables to be prepared for the final Clinical Study Report.

The proposed FAST Uveitis Trial is a block randomized, observer-masked, comparative effectiveness, Phase III clinical trial to compare the efficacy of mycophenolate mofetil (CAS 128794-94-5) to methotrexate (CAS 59-05-2) for the treatment of non-infectious uveitis requiring steroid-sparing therapy.

The content of this Statistical Analysis Plan meets the requirements stated by the US Food and Drug Administration and conforms to the American Statistical Association's Ethical Guidelines.[1, 2]

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- FAST Uveitis Trial Manual of Operations
- ICH Guidance on Statistical Principles for Clinical Trials[2]
- Statistical Analysis Plan [redacted]
- Statistical Analysis Plan [redacted]

The planned analyses described in this Statistical Analysis Plan will be included in future manuscripts. Note, however, that exploratory analyses not necessarily identified in this Statistical Analysis Plan may be performed to support the analysis. All post-hoc or unplanned analyses which have not been delineated in this Statistical Analysis Plan will be clearly documented as such in the final Clinical Study Report, manuscripts, or any other document or submission.

The final SAP is subject to the approval of an appointed Data and Safety Monitoring Committee.

The following individuals contributed to this document: [redacted]

2 Investigational Plan

2.1 Study Design

The proposed study is an international, multicenter, block randomized, observer-masked, comparative effectiveness clinical trial to determine which treatment, methotrexate or mycophenolate mofetil, is more effective as first-line corticosteroid-sparing treatment for patients with non-infectious intermediate, posterior and panuveitis requiring corticosteroid-sparing therapy.

Full details which specify the definition of treatment success are given in the FAST Manual of Operations.

2.2 Study Population

Eligible volunteers diagnosed with non-infectious uveitis who have given informed consent will be enrolled in this trial. Specific eligibility and exclusion criteria are given in the FAST Manual of Operations. The proposed study schedule is listed in the FAST Manual of Operations.

2.3 Specific Aims

2.3.1 Specific Aim 1

Primary Objective. The primary objective of the study is **to establish which immunosuppressive treatment, methotrexate or mycophenolate mofetil, results in a higher rate of corticosteroid-sparing treatment success, on an intent to treat basis.** Specifically, we will compare the fraction of subjects who achieve treatment success at six months (as defined in the Manual of Operations Section 2.5.1) between the two groups.

Primary Outcome. The primary outcome for Specific Aim 1 will be the difference in the proportion of patients assigned to mycophenolate mofetil vs. methotrexate who achieve treatment success (as defined in the Manual of Operations Section 2.5.1).

Patients who experience success at 6 months with the drug to which they were originally randomized (in Specific Aim 1) will continue on the same drug for an additional 6 months. This will be called Phase I (6-12 months). Patients will then be seen every 3 months (and will be examined at 9 months and at 12 months), until success at 12 months or treatment failure at any time. Patients who fail treatment before 12 months with the initial drug will be removed from the study and treated according to best medical judgment.

Secondary Objectives

- To determine whether patients exhibit a difference in time to control of inflammation within the first six months.
- To determine whether patients exhibit a difference in time to corticosteroid sparing control of inflammation within the first six months.
- To evaluate the proportion of patients achieving treatment success at 5 months and sustaining, for at least 28 days, to 6 months.
- To evaluate a difference in control of inflammation in the posterior/pan anatomic locations only, assessed at by six months.
- To evaluate a difference in control of inflammation in the interior and anterior/intermediate anatomic locations only, assessed at by six months.
- To determine whether there is a change in best spectacle-corrected visual acuity at six months.
- To determine whether patients treated exhibit a difference in health related quality of life at six months.
- To determine if there are differences in discontinuing treatment due to each of the following reasons: safety, intolerability or lack of efficacy at six months.
- To determine whether patients exhibit a difference in the proportion of patients having macular edema at 6 months
- To determine whether patients exhibit a difference in macular thickness at 6 months
- To determine whether patients exhibit a change in vitreous haze, assessed clinically by the NEI and Davis scales at 6 months
- To determine whether patients exhibit a change in vitreous haze, assessed by the photographic grading of haze by the NEI and Davis scales at 6 months.
- To determine the proportion of patients discontinuing due to intolerability at six months.
- To determine the rate of adverse events experienced at six months.
- To determine the proportion of patients discontinuing due to serious adverse events at six months.
- To determine whether patients exhibit a change in quality of life at six months.
- Tabulate the occurrence of dose reduction used in immunosuppressive treatment (see Manual of Operations Section 3.1 for dose reduction guidelines).
- To determine efficacy of treatment in Vogt-Koyanagi-Harada (VKH) patients at six months.
- To determine the proportion of patients beginning with at least 2+ inflammation in anterior chamber cells and experience at least a 2-step reduction (i.e. decreasing from 2+ to 0.5+; 3+ to 1+; 4+ to 2+).
- To determine the proportion of patients beginning with at least 2+ inflammation in vitreous haze and experience at least a 2-step reduction (i.e. decreasing from 2+ to 0.5+; 3+ to 1+; 4+ to 2+0.

- To evaluate a difference in treatment success controlling for vasculitis at baseline, assessed at six months.
- To explore the use of a dynamic process model (such as a Hidden Markov model) to assess differences in control of inflammation.

- VKH) patients at six months.

  - Proportion of patients who started with at least 1+ inflammation levels in anterior chamber cells who achieve a decrease to 0 level of inflammation in anterior chamber cells.
  - Proportion of patients who started with at least 1+ inflammation levels in vitreous haze who achieve a decrease to 0 level of inflammation in vitreous haze.

All the above analyses will be examined at the end of Phase I (6-12 months), in addition to the following:

• To determine whether patients exhibit a difference in the probability of controlling inflammation with complete discontinuation of steroids at twelve months in Phase I.

2.3.2 Specific Aim 2

Primary Objective. The primary objective of this aim is to evaluate the clinical efficacy of switching agents as rescue therapy after initial treatment failure.

Patients who experience treatment failure (as defined in the Manual of Operations) with the drug to which they were originally randomized in Specific Aim 1 will discontinue the current treatment and be administered rescue therapy with the second drug (in a masked fashion). This will be called Phase II. Treatment failure with the first drug is defined as the inability to continue taking the drug to which the patient has been randomized, either due to intolerability, safety concerns, or lack of efficacy.

Upon declaration of treatment failure, the patient will be automatically screened for Aim 2. If eligibility criteria are met, the second treatment will be administered and data will be collected for the Phase II baseline visit. Patients will then be seen every 4 weeks until 6 months or until treatment failure with the second drug. Treatment failure and success will be defined as in Aim 1. Patients who fail treatment before 6 months with the second drug will be removed from the study and treated according to best medical judgement.

Primary Outcome. The primary outcome is the fraction achieving treatment success at 6 months after starting Phase II. Treatment success is defined as in Aim 1 and described in the Manual of Operations Section 2.5.1.

Secondary Objectives. All of the secondary 6 month objectives listed for Aim 1 will be examined for Aim 2.

2.4 Randomization

2.4.1 Stratification between sites

Patients will be recruited from nine sites: [redacted] (see Manual of Operations Section 2.2 for details). Patients will be randomized to two treatments (arms): methotrexate (X) or mycophenolate mofetil (Y). The treatment protocols are specified in the FAST Uveitis Trial Manual of Operations.

Within each site, assignments will be conducted using a block randomization scheme with randomly varying block sizes.

2.4.2 Randomization list

Lists of sequential randomization assignments will be prepared for each site. The randomization lists consist of a unique identifier for each patient, together with the assignments to treatment arms. The assignment of patient ID numbers and randomization is thus performed on enrollment.

The randomization lists for sites will be prepared by the [redacted] site (see Section 10.3) and sent to the Emergency contact at each site to be used only in case emergency unmasking is needed for patient safety.

They will also be sent to hospital/clinic staff who are responsible for telling the study coordinators the treatment assignment for each patient after the patient is enrolled and the study ID has been assigned. At these sites she will verify patient treatment assignment as a quality assessment.

A backup copy of the full randomization list for all four sites will be maintained by [redacted] This list will be maintained as a hard copy stored in a locked file cabinet at the [redacted] site, and to be used only in case emergency unmasking is needed for patient safety.

Distribution of the randomization list to [redacted] will be accomplished using the [redacted] encrypted email provision. Email is encrypted using the Advanced Encryption Standard (NIST FIPS 197) whenever the first four characters of the subject line are `PHI:` The sender is notified when the recipient receives a secure email; the recipient receives a notification of a secure email and can view it using the [redacted] Secure Messenger website. We have successfully used this method in previous clinical trials [redacted]. The randomization lists will each contain more randomization assignments than needed. Successively recruited patients will receive sequential

assignments from the list. The long list provides a measure of added safety in case one of these sites recruits far more patients than expected relative to the other site.

As discussed below, the randomization lists will be provided as Excel® worksheets. No technical knowledge will be required to use these lists.

Update: starting 18 January 2017, all patients will be randomized using the REDCap database. Coordinators can access only the randomization lists for their site. When patients are enrolled, the ID is logged in REDCap and the system provides the medication assignment. All emergency contacts have access to the REDCap database for their site in case of an emergency when unmasking is needed for patient safety. The REDCap database contains assignments for all previously enrolled patients. All previous randomization lists were deemed void and were destroyed. Each site submitted a certification of destruction form.

2.4.3 Block randomization

We will utilize a permuted block randomization scheme with a randomly varying block size (within each study site) to protect the integrity of the assignment masking.[3] Any particular block size will be unknown to the study investigators. We will choose randomly varying block sizes, picking a block of size 4 with probability 2/3 and a block of size 6 with probability 1/3. Individuals have a higher probability of being in a block of size 6 because the blocks are larger. Many other choices would serve equally well. Given the block size, a random permutation of assignment orders will be generated.

2.4.4 Unique patient identifiers

Unique patient identifiers will be generated as follows. The first character will be a number: [redacted] The next character is a checksum character, which will be a single letter. The last three characters will be sequential digits beginning at 001. An example identifier is 4J101; all identifiers have exactly five characters, and no other [redacted] study uses this format.

2.4.5 Random number generation

The choice of a random number seed determines the specific sequence of random numbers that will be produced by the random number generator. Once the seed is determined, the randomization assignments for all sites are determined. Details are given in the Appendix.

2.4.6 Provision of randomization list

Everyone to whom the randomization list should be provided (for each of the four sites) will receive it in the following format: a Microsoft Excel® spreadsheet containing the following columns: (1) the unique study identifier assigned to the patient (see Section 2.4.4), (2) an empty field into which the date of randomization may be entered (relevant only for the hospital/clinic staff holding the randomization lists), (3) the study drug assignment, written out in full as

`Mycophenolate` or `Methotrexate`. As discussed in Section 2.4.2, these lists will be treated confidentially.

Update: As of 18 January 2017, all randomization lists are electronic on REDCap. Once a patient is enrolled, the study coordinator logs the patient in the database and the system reveals the drug assignment, written out in full.

2.4.7 Quality assurance

Three quality assurance steps for the randomization list preparation are conducted. First, the software will have been tested during previous studies [redacted]. Second, the software that generates the assignments verifies approximate balance of subjects in each group before writing the Microsoft Excel® files. Each file will contain the study site as the first line. Finally, the output files will be visually inspected. The software and procedures have already been developed and successfully used in previous studies.

2.4.8 Summary of disposition of randomization list

The following individuals will receive a copy of the randomization list:

Emergency Contact Personnel

[redacted]

*Emergency contact persons who will consult the list only in case of an emergency in which unmasking is necessary for patient safety and [redacted] on the DCC cannot be reached.

Data Coordinating Center (DCC) Personnel

[redacted]

Clinic/Hospital Staff

[redacted]

* [redacted] will act as study coordinator to [redacted] patients, as well as Coordinating Center Manager overseeing all other sites. [redacted] will have access to the randomization lists for other sites, in order to check patient treatment assignment as a quality assessment and manage distribution of medications to all sites.

2.5 Masking

The clinical examiners, refractionists, OCT technicians, fundus photographers and fundus graders will be masked to the treatment assignment. Note that only the individuals listed in Section 2.4.8 will have copies of the randomization list. Full details of procedures to maintain masking as well as for potential unmasking in the event it becomes necessary for safety reasons are provided in the Manual of Operations. Principal Investigator [redacted] is masked.

3 Statistical Considerations

3.1 Baseline characteristics

At baseline, each eye (1) may be fully able to be assessed, (2) it may be possible assess part of the eye, but not be possible to assess the entire eye, or (3) it may not be possible to assess any of the eye. For each eye for which some assessment is possible, either (1) the eye showns no signs of uveitis, or the eye may show some signs of uveitis, but fail to meet the severity criteria (1+ anterior chamber cells, vitreous haze or no active retinal/choroidal lesions, as defined in the Manual of Operations), or (2) the eye meets the severity criteria as defined in the manual of operations. Some patients are monocular at baseline, one eye being either absent, or exhibiting such disease as to preclude the possibility of ever assessing the eye (i.e. phthisis).

For this trial, we summarize the above possibilities as follows. Each eye (OD or OS) may be classified into one of the following types at baseline:

A. Eye fully assessible, does not meet the severity criteria as defined in the MOP
B. Eye partially assessible, does not meet the severity uveitis criteria in the assessible region
C. Eye fully assessible, meets severity criteria
D. Eye partially assessible, meets severity criteria in assessible region
E. Eye absent or too diseased to ever assess

Patients, not eyes, are the unit of assignment and of randomization. Thus, there are twenty-five possible types of patients. A patient is required to have at least one eye which meets severity criteria for uveitis, and which can be completely assessed. Eligibility is summarized in the following table; cells indicate the possibility of enrollment for a patient whose right eye classification corresponds to the row and whose left eye classification corresponds to the column (A-E being defined in the previous paragraph).

	OS: A	OS: B	OS: C	OS: D	OS: E
OD: A	Not eligible	Not eligible	**Eligible**	Not eligible	Not eligible
OD: B	Not eligible	Not eligible	**Eligible**	Not eligible	Not eligible
OD: C	**Eligible**	**Eligible**	**Eligible**	**Eligible**	**Eligible**
OD: D	Not eligible	Not eligible	**Eligible**	Not eligible	Not eligible
OD: E	Not eligible	Not eligible	**Eligible**	Not eligible	Not eligible

Assessment and follow-up depends on the status of the eye. Eyes classified as type E above are recorded as such at baseline, and never provide eye outcome related data. Because (a) inability to assess parts of the eye could be related to the progression of disease, but (b) inability to assess in the absence of signs of disease cannot be considered evidence of treatment failure, we use the following table to summarize how success at six months will be scored. In this table, the row corresponds to the status of an eye at baseline, and the column to the status of the eye considering the primary outcome of success at six months.

	Month 6: A	Month 6: B	Month 6: C	Month 6: D	Month 6: E
Baseline: A	Success	See below**	Fail	Fail	Fail*
Baseline: B	Success	See below**	Fail	Fail	Fail*
Baseline: C	Success	See below**	Fail	Fail	Fail*
Baseline: D	Success	See below**	Fail	Fail	Fail*
Baseline: E	NA	NA	NA	NA	NA

Specifically, note that an eye which is fully assessible at six months and which does not meet the specific criteria for failure of control is always considered a success. Eyes which are fully or partially assessible and which meet any of the criteria for failure are always considered to have failed. However, eyes which are only partially assessible but which meet no criteria in the assessible region may be scored successes or failures depending on their baseline status (see next paragraphs below). Eyes which were present at baseline but which are missing at the end of the study are listed as Fail* in the table; we propose to consider such eyes to have failed unless a specific reason demonstrates that the loss of the eye was completely unrelated to the presence or progression of disease.

The primary analysis is at the patient level. Both eyes must meet the success criteria for the patient to be considered a success.

****Incompletely assessible eyes.** Uveitis assessment for this purpose is based on (i) assessment of anterior cells, (ii) vitreous haze, and (iii) retinal or choroidal lesions. In the pilot study, (iv) assessment of vitreous cells was also used. We will have longitudinal measurements of inflammation according to the following schedule: anterior chamber cells, vitreous haze and

active retinal/choroial lesions will be measured at Baseline, Week 2, Month 1 and every subsequent 4 weeks until the 6 month assessment (Phase I or Phase II) or 9 and 12 month assessment (Phase I 6-12 months).

Each of these (including the binary assessment of the presence of retinal or choroidal lesions) may be considered an ordinal variable, with relevant threshold values for each (used in determining eligibility for enrollment, or success in therapy).

Scoring of incompletely assessible eyes is governed by the following guiding principles:

1. In some patients, the front of the eye may be assessible, but the back of the eye cannot be examined and assessed clinically (even though the patient can still see out of the eye).
2. Worsening of uveitis may render it harder to assess the back of the eye, so that information cannot be considered missing at random in general.
3. Many uveitis patients have at least one eye which cannot be fully assessed, because of the progression of the disease itself. Excluding such patients or eyes completely is undesirable.
4. Treatment of uveitis will not reverse the damage which makes it difficult to assess all parts of the eye.
5. Worsening of cataracts may also cause an eye to become incompletely assessible, so that a change in assessibility status does not always indicate a worsening of uveitis or a failure of uveitis treatment.

We chose the following simple, but conservative, approach to scoring such eyes. For an incompletely assessible field (anterior cells, vitreous haze, or presence of retinal or choroidal lesions) at any time, the worst value seen until that time will be assigned for the unavailable measurement. Thus, a decreasing ability to assess regions of the eye—in the absence of evidence of inflammation or uveitis criteria—does not imply failure of therapy. Decreasing ability to assess eyes which had signs of uveitis will imply failure of therapy. It is understood that this procedure will misclassify some events such as: (i) an eye which had vitreous haze or a retinal or choroidal lesion at baseline, which resolved over the course of the six months, and for which a progressing cataract rendered the posterior of the eye impossible to assess, will be scored as a failure, or (ii) an eye for which the posterior region had no inflammation at baseline, which then became impossible to assess, and then which develops posterior inflammation which cannot be seen, will be scored as a success. We believe such misclassifications will be infrequent.

Selected secondary outcomes, including vision, macular edema, time to control of inflammation, will be analyzed at the eye level. All eyes that meet inclusion criteria of inflammation at baseline will be included in this analysis. Linear or generalized linear mixed modeling will be conducted (see below for details).

The following is a brief summary of general guiding principles.

- For the primary outcome, if any portion of the eye cannot be assessed at baseline, and it *still cannot be assessed at Visit 6 or Visit 12*, if all other markers of success are met, this portion of the eye would be considered to have had successful therapy.
- For the primary outcome, if any portion of the cannot be assessed *by Visit 6 or 12* and this

same portion of the eye was *completely assessable* at baseline, if all other markers of success are met, then the last worst observation for this eye would be carried forward and used at the assessment of this eye portion.

- For the primary outcome, if an eye *becomes missing by Visit 6 or 12,* and it is related to uveitis (regardless of its disease status at baseline) if all other markers of success are met, this patient should be considered a failure.

3.1.1 Demographics and Patient History

All demographic and history variables (in particular, age, gender, occupation, and ethnicity/national origin) determined at enrollment will be summarized by counts and percentages tabulated by treatment assignment.

3.1.2 Prior and concurrent medication

We will present the oral and topical corticosteroid doses at presentation (specifically, the current daily dose at baseline) and other medications by randomization arm and study site.

3.1.3 Baseline comorbidities and history

Clinical variables at baseline (in particular, anatomical site and vasculitis) will be presented by gender, age, and study site. We will also tabulate the presence of associated systemic disease at baseline. Anatomical site will be classified at the patient level as site of most serious involvement. For example, if a patient has anterior inflammation in the right eye and panuveitis in the left, they would be classified as a panuveitis patient.

3.1.4 Compliance

Compliance is assessed through patient self-report and regular pill counts by study coordinators at each visit when patients bring in their medications.

3.2 Analysis

3.2.1 Summary of Principal Outcome Variables and Regression Variables

Variables

- Primary outcome: Patient treatment success by six months (see MOP, Section 2.6)
- Patient treatment success at twelve months (Phase I)
- Successful control of inflammation in both eyes by twelve months, with complete discontinuation of corticosteroids
- Best spectacle-corrected visual acuity, at baseline and at the time of failure or six months (two observations per patient)
- Time to corticosteroid sparing control of inflammation (6 months and 12 months)
- Change in health related quality of life subscores (PCS and MCS) from SF-36 and Vision Related Quality of Life from NEI-VFQ-25 and IND-VFQ at six months and twelve months

- Reason for discontinuation of therapy (if applicable) at six months and twelve months
- Macular thickness at baseline, and at six months and twelve months
- Presence of macular edema at six months and twelve months
- Vitreous haze assessed clinically by the NEI and Davis scales at baseline, six months, and twelve months
- Vitreous haze as assessed by the photographic grading of haze by the NEI and Davis scales at baseline six months and twelve months
- The proportion of patients discontinuing due to serious adverse events at six months and twelve months
- Tabulate the occurrence of dose redution used in immunosuppressive treatment.
- Treatment efficacy of VKH patients at six months and twelve months
- Treatment efficacy of patients with vasculitis at enrollment

Note that the presence of cataracts renders assessment of vitreous haze more difficult. Vitreous haze measurements in the presence of certain cataracts will be considered less reliable, and this will be considered in statistical modeling. Analyses will be repeated for differing assumptions about this bias. A maximum likelihood latent variable model will be considered, in which a true underlying vitreous haze level predicts an observed value. The observation model will include a higher probability of yielding a large observed value in the presence of a cataract.

Major independent variable of interest

- Treatment assignment (methotrexate or mycophenolate mofetil)

Additional regression variables used in selected analyses

- Anatomic location (coded dichotomously as either intermediate (code 0) or as being either posterior uveitis or panuveitis (code 1))
- Country
- Study site
- Gender
- Age
- Baseline quality of life (health and vision related)
- Baseline best spectacle-corrected visual acuity, vitreous haze, macular thickness
- Vasculitis

Inclusion of Data

- Data will be included for all outcomes within the window peroid of -2 weeks to +4 weeks around the 6 Month Visit date for Phase I (0-6 months).
- Data will be inlcuded for all outcomes within the window peroid of -2 weks to +4 weeks around the 12 Month Visit date for Phase I (6-12 months).
- Data will be included for all outcomes within the window period of -2 weeks to +4 weeks around the 6 Month Visit for Phase II (0-6 months).

3.2.2 Specific Aim 1

Primary Analysis.

The primary analysis will be a logistic regression model, predicting treatment success at 6 months based on treatment arm. We wish to aggregate sites within countries, and countries within treatments provided we find no evidence of heterogeneity of sites or countries.

Specifically, the pre-specified primary analysis will be performed as follows. We denote the assignment group of patient *i*, *i*=1,...,*N* (where *N* is the number of subjects) by X_i^1, which equals 0 when the patient is in the methotrexate group and 1 when the patient is in the mycophenolate mofetil group. The outcome variable is Y_i, which is 1 if treatment success of patient *i* is achieved by six months, and 0 otherwise. The variable is missing if the patient is lost to follow-up or drops out of the study for reasons other than discontinuation due to intolerance or adverse events; if the patient discontinues the medication due to intolerance or adverse events such as abnormal laboratory findings, the value is 0.

The primary analysis is a logistic regression with treatment arm as a predictor. For the primary analysis, we propose to use study site as a *random effect* (random intercept model). The null hypothesis is that the regression coefficient for treatment arm equals zero, which will be tested using a likelihood ratio test with one degree of freedom. We will also fit the following models: (a) a model including drug, site, and drug × site interaction, (b) a model including only drug and site, (c) a model including only drug and country, and (d) a model with drug, country, drug-country interaction, and site within country. Countries or sites with fewer than three observations will be pooled together. Provided there is no evidence of treatment × site interaction or treatment × country interaction, we will report pooled treatment effects and confidence intervals. In the event evidence suggests a difference between treatment sites, we will report treatment effects by site, and repeat the analysis excluding particular sites. Similarly, evidence of a treatment × country interaction will lead us to report treatment effects and confidence intervals by country.

Simulations suggest that use of a model containing interaction terms between site or country and treatment for the primary analysis is undesirable. Such a procedure results in modest loss of power unless the treatment effect is of opposite sign in different sites or countries.

The hypothesis test is to be two-sided with alpha of 0.05. We propose to compute the P-value by permutation testing, based on the block randomization scheme.

Prespecified Subgroup Analysis.

The prespecified subgroup analysis will test the hypothesis that there is a treatment effect separately in each anatomic group, using a logistic regression model.

We denote the two anatomic groups by X_i^3, which equals 0 when the patient is in the intermediate group and 1 when the patient is in the posterior/pan group. In the intermediate subgroup, we plan to determine whether there is evidence of a treatment effect (regardless of the effect in the posterior/pan group). Specifically, we will conduct this analysis in two ways: anatomical site at enrollment (split into three categories: anterior, anterior/intermediate or intermediate only, and posterior/panuveitis), and anatomical location by history (split into two

categories: anterior/intermediate or intermediate only, and posterior/panuveitis). Anatomical location by history is considered the prespecified analysis; anatomical location at enrollment will supplement this finding.

We propose to proceed as follows. We propose to begin with Equation (1), adding terms $\beta_3 X_i^3 + \beta_{13} X_i^1 X_i^3$ for anatomic location and for treatment-location interaction. We wish to test the hypothesis that $\beta_{13} = 0$, i.e. that there is a difference in treatment efficacy between the anatomic locations, controlling for country. Alternative models will be fit in which the country, site, and treatment x country terms are omitted.

We will also report relative risks in each substratum, using relative risk regression.

Additional analyses will add gender and age to the predictors. The entire analysis will be repeated for each gender, and separately for each country (US and India) and anatomic location.

Planned Secondary Analyses.

Each of the following secondary analyses is designed to test the hypothesis that treatment assignment affects a given outcome, after controlling for selected covariates. All analyses will be repeated without controlling for covariates (i.e., using treatment assignment as the only predictor). In all cases, appropriate regression diagnostics and/or goodness of fit tests will be performed (further details are given below). In addition, we will compute jackknife influence statistics in each analysis, to determine whether or not any single observation (eyes or patients, as appropriate) have an undue effect on the final conclusion. All models with site effects will be repeated omitting this effect, and again repeated including a treatment-site effect, and with country and/or treatment by country interactions (i.e., pooling within countries when appropriate). When reporting findings, care will be taken to distinguish the single prespecified test from supplemental tests (whether prespecified or unprespecified); exploratory analyses will always be labeled as such. All alpha levels are to be two-sided.

1. *Twelve-month endpoint for successes*. We propose to compare the proportion who maintain successful control for twelve months (i.e. the outcome is the proportion who have achieved control in all study eyes both at the six month visit and at the 12 month visit) between the two study arms. Per protocol, patients with successful control of their inflammation at 6 months remain on the same treatment until 12 months. We will use the same statistical model (and Wald procedure) as for the primary analysis. We test the hypothesis that the coefficients for treatment assignment and treatment assignment/anatomic location interaction both equal zero.

2. *Time to corticosteroid sparing control of inflammation*. We propose to use a Cox proportional hazard model with the outcome being the time to (1) first steroid-sparing control, and separately (2) first control of inflammation, with treatment assignment (and interaction) as the predictors. Time to first steroid-sparing control is the principal prespecified analysis here; alternative approaches will be conducted for additional insight and as sensitivity analyses. We will supplement this analysis with a parametric survival analysis using the Weibull distribution and also with a gamma distribution (note that individuals may drop out at any time, not just at the monthly visits), and with a method treating the time to success as interval censored. The outcome for this analysis is a single number for each patient (not for each eye). The primary statistical

result will be the Wald test for the treatment assignment coefficient. We will repeat the analysis using study site as a fixed effect in this model (and as a sensitivity analysis, will explore random-effects survival analytic methods which are becoming available, see Pankratz et al.).[6] In supplementary analyses we will include age and anatomic location as additional covariates.

3. *Country and site within country.* We denote the country by X_i^2, which will be 0 for US locations and 1 for Indian locations; X_{i1}^4 is 1 only for patients in the second Indian site and 0 otherwise, while X_{i2}^4 is 1 only for patients in the second US site and 0 otherwise. As mentioned under the Primary analysis, we propose to fit models with country only, drug by country interaction, and with a drug by country interaction, including site within country as well. Analysis will be conducted within each site, then pooling the sites within country together.
Further details regarding pooling across centers are provided above under the main prespecified analysis.

4. *Best spectacle-corrected visual acuity (BSCVA).* The primary outcome variable for this secondary outcome will be the change in best spectacle-corrected visual acuity from baseline to final (as defined in the FAST MOP, i.e. for those who successfully control inflammation as defined in the MOP, or at the time of failure for those who fail; MOP, Section 2.6). Visual acuity change scores are available for both eyes for each patient.

The primary analysis will use a linear mixed-effects regression, where the outcome variable is the change in BSCVA in each eye, using treatment assignment as a statistical predictor (regressor, independent variable); a random effect will be used at the individual level, because of the possibility that changes in the two eyes from a given patient are correlated. In a supplementary analysis, we will include as predictors (independent variables) anatomic location of uveitis, interaction between anatomic location and treatment assignment, and the study site, together with a random effects for patient. We will fit these models using maximum likelihood (R procedure lmer) and use likelihood-ratio tests to test the hypothesis that treatment assignment affects BSCVA change. Only eyes that are eligible and meet inflammation criteria at baseline will be included in this analysis. If at a given visit, vision cannot be assessed, we will carry the last observation forward. Additional sensitivity analyses for missing data will be used (including mixed effects models controlling for time, including all data from an individual).

Also, if there is no eye at Month 6 to assess, the patient will be given a logMAR value of 2.0.

Because of the possibility that the outcome variable (BSCVA change score) will exhibit non-normality, we will repeat the analyses using transformations of the outcome data (including power and log transformations, or more general monotone transformations).

Additional analyses will be performed using age, gender, ethnicity, and the steroid dose at each month as predictors.

An additional supplemental analysis will be conducted using final BSCVA (instead of the change score) as the outcome, and including baseline BSCVA in each eye as a predictor, using methods otherwise identical to those above.

5. *Quality of life.* We will also use a linear mixed model to assess health-related quality of life, measured by the SF-36 questionnaire (PCS and MCS scores) and vision related quality of life NEI-VFQ-25 and IND-VFQ at 6 months or at the time of failure, as described in the Manual

of Operations. Predictors will be baseline quality of life, age, gender, ethnicity, study site (as a random effect), and treatment assignment, and we will test the hypothesis that the regression coefficient corresponding to treatment assignment equals zero using the Wald t-test. Similar assessments will be performed for vision-related quality of life questionnaires.

6. *Reason for discontinuation.* Individuals who discontinue study medication may do so due to inability to tolerate side effects, due to lack of efficacy, or for safety reasons. The outcome variable is whether the person discontinued due to intolerance, discontinued due to lack of efficacy, discontinued due to safety, or did not discontinue the medication. Because study site may be an important factor, we will use polytomous regression to model the discontinuation result as a function of treatment assignment (using a fixed effect for study site).[7] If evidence is found that treatment assignment influences discontinuation result, further analyses may be conducted to determine whether or not treatment assignment is associated with discontinuation due to intolerance, lack of efficacy, or to safety, or some combination of these. We propose to classify all individuals in a two by four table according to treatment assignment and discontinuation (not discontinued, discontinued due to intolerance, discontinued due to lack of efficacy, discontinued due to safety) and conduct the Fisher's exact test (in its $r \times c$ form). The use of an overall test prior to further analysis is designed to protect the overall error rate.

7. *Successful control of inflammation with complete discontinuation of steroids (Phase I 6-12 months).* Some individuals may be able to taper completely off of steroids while maintaining control of inflammation. The outcome variable is the fraction of individuals achieving such control in both eyes (out of the number of individuals starting therapy). We propose to compare this fraction between the two treatment groups using logistic regression. The statistical analysis will otherwise be identical to the primary analysis.

8. *Macular edema.* We wish to compare the fraction of patients with macular edema at 6 months, between the two treatment arms. This will be conducted using the Fisher exact test, with a two-sided test at alpha of 0.05. Supplementary analyses will be based on logistic regression using the presence of macular edema as a binary outcome variable, with regressors ("independent variables") of treatment arm and anatomic location. Further analyses (including other baseline covariates or other subsets) will be labeled as exploratory.

9. *Change in Macular thickness.* We propose to test the hypothesis that macular thickness is different in the two treatment arms, at 6 months. We propose to model the macular thickness at 6 months using two regressors: treatment arm and baseline thickness. We will test the hypothesis that treatment arm is associated with final macular thickness, using the T-test of the regression coefficient for treatment arm in the model including baseline thickness as a second covariate (two sided using α=0.05). We will examine residuals for normality and homoskedasticity, and prepare residual vs fitted value plots. Standard transformations will be used in case of evidence that the assumptions have been violated.

We will also look at change in macular thickness in only patients who had macular edema at Baseline.

10. *Bayesian analysis.* Prior to data collection, we will elicit a Bayesian prior for the effect size (difference between the two treatment arms) from a group of uveitis experts, using methods our group has previously applied to the [redacted]. The likelihood

function corresponding to Equation (1) will be used to yield a posterior distribution for the effect size. Quantiles of this distribution will be reported, together with sensitivity analyses (with respect to model choice, influential observations, and prior distribution).

11. *Alternative definitions for success*. Other definitions will be examined: (i) changing the algorithm for assigning values for unobservable uveitis examination fields (anterior cells, vitreous haze, retinal/choroidal lesions) so that any worsening of ability to assess the eye for any reason is scored a failure, or (ii) use of vitreous cells in the definition of uveitis.

12. *Change in vitreous haze* will be assessed using clustered polytomous logistic regression, using baseline vitreous haze as a covariate and follow-up time. Vitreous haze is an ordinal outcome variable. A random effect is needed because the two eyes of a given patient cannot be treated as statistically independent. Both the NEI and Davis scales will be analyzed, for both direct observations and photographic grading. Treatment assignment will be a covariate. Alternative methods will be examined, including a simple McNemar test in which we dichotomize vitreous haze assessments at baseline and at the final observation.

13. *Rate of adverse events* and the proportion of patients discontinuing due to adverse events will be tabulated by treatment assignment, age, and gender; confidence intervals will be reported.

14. *Treatment efficacy in VKH patients* will be assessed as a planned subgroup analysis. Note that anatomic location is also a planned subgroup analysis, as well as study site and study country (aggregating all sites within each country).

15. *Dose reduction* will be compared by arm using logistic regression based on treatment, and other covariates as needed.

16. If no difference is found for the primary outcome comparing treatment success between arms, we will assess whether methotrexate is non-inferior to mycophenolate mofetil, assuming a 10% non-inferiority margin. The non-inferiority margin of 10% is clinically meaningful and was based on investigator consensus. Methotrexate will be considered non-inferior to mycophenolate if the lower limit of the 95% CI for treatment success at 6 months is less than 10%. This analysis will be conducted because mycophenolate mofetil is much more expensive than methotrexate, so a determination that methotrexate is not inferior has clinical implications. We are interested in a one-sided comparison given the cost differential between methotrexate and mycophenolate mofetil.

17. Additional exploratory modeling will be conducted using clustered multinomial logistic regression using all time points and all observations of anterior chamber cells, vitreous haze, and retinal/choroidal lesions.

3.2.3 Specific Aim 2

Primary Analysis.

The primary analysis will compare the proportion of successes between (a) patients treated with mycophenolate mofetil following failure on methotrexate and (b) patients treated with methotrexate following failure on mycophenolate mofetil.

Specifically, we will conduct a logistic regression in which success or failure will be the outcome, and the predictors (regressors, independent variables) will be treatment group and reason for failure of the first drug (lack of efficacy vs any other reason). Supplementary analyses will include anatomic location (intermediate vs posterior/pan) and country. We will test the hypothesis that the coefficient for treatment group equals zero (i.e., that mycophenolate mofetil rescue after methotrexate failure has the same result as methotrexate rescue after mycophenolate mofetil failure). All alpha levels will be two-sided.

It is important to emphasize that estimation of the success rate of the second drug following the failure of the first is a central goal of the trial, arguably as or more important than the hypothesis test itself. The success rates and confidence intervals will be presented regardless of the results of the hypothesis test.

Secondary Analyses.

The following secondary analyses are planned.

We will also present the estimated success proportion in both treatment groups, together with the 95% confidence intervals. The two groups are the individuals who were undergoing methotrexate rescue therapy after mycophenolate mofetil, and those who were undergoing mycophenolate mofetil rescue therapy after methotrexate. Logistic regression will also be used to adjust for study site.

The second prespecified analysis will compare the rate of success between rescue patients and first-line patients, using logistic regression; we will test the hypothesis that the coefficient for rescue/initial equals zero. A supplemental variation of this analysis will include an additional predictor for whether the patient was on rescue therapy due to lack of efficacy, lack of safety or intolerance, or anatomic location. Two separate analyses are planned, each with an alpha of 0.05.

Exploratory and descriptive analyses of covariates such as reason for failure of the initial regime, age, disease (e.g., VKH), and affected region of the eye, will be presented.

3.3 Transformations and model adequacy

3.3.1 Primary Analysis

Sensitivity analyses based on modeling the individuals lost to follow-up will be conducted, however; we will determine how much of a treatment effect there would have had to have been in the patients lost to follow-up, for the results of the main hypothesis test to change.

3.3.2 Unspecified secondary analyses

Unprespecified analyses may be conducted following the primary analysis and will always be reported as such. Analyses will always be repeated including age and gender, in particular.

3.3.3 Model validation and sensitivity

In all cases, standard statistical procedures will always be followed to ensure that no evidence indicates a violation of the assumptions underlying the statistical models used. Specifically, we note the following: secondary analyses based on the use of age as a continuous predictor in logistic regression models with treatment success as an outcome will be assessed using the Hosmer-Lemeshow goodness-of-fit test. Linear models will always be assessed using residual plots (residuals vs. predicted values, and QQ plots), together with tests for normality (Anderson-Darling and Shapiro-Wilk procedures). For mixed models, we will examine marginal residuals, conditional residuals, and EBLUPs.[8] When modeling binary outcomes (using clustered logistic regressions), we will repeat analyses using a probit link as a check on robustness; we will also examine the Pearson goodness of fit statistic.[9] Jackknife influence estimates will be used in all analyses; single observations that could change the conclusions will always be reported. Analyses in which time to response is used as the outcome variable (in which Cox regression is conducted) will be supplemented with the Gill-Schumacher procedure for assessing the adequacy of the proportional hazards assumption for Cox regression.[10] Analyses in which our primary interest in in final outcomes will still be repeated using all available data (at all time points).

Failure of the modeling assumptions (such as normality) will result in conducting additional analyses. First, for continuous outcome variables, we will undertake normalizing or variance-stabilizing transformations of the outcome variable (such as power transformations). Second, robust procedures will be used to estimate the standard errors whenever possible. Third, the use of bootstrap procedures, when applicable, will be considered in estimation of standard errors.[11]

3.4 Sample Size Evaluation

3.4.1 Primary Calculation

The sample size for the trial will be 216 subjects, which we anticipate will provide approximately 80% power to detect a difference of 20% in the proportion of patients achieving control of inflammation at six months between the methotrexate and mycophenolate mofetil groups.

This sample size was determined based on the primary objective (superiority comparison of mycophenolate mofetil to methotrexate) and primary endpoint (treatment success). We assumed an effect size of 20%, as this was deemed to be clinically meaningful, and well within the distribution of the investigators' prior beliefs from published retrospective studies.

An approximate sample size is provided by the formula

$$2N=\frac{4(Z_{\alpha}+Z_{\beta})^{2}\bar{p}(1-\bar{p})}{(p_{c}-p_{i})^{2}} \qquad (5)$$

(see Friedman et al. 2010), where α is the significance level (0.05, two sided), β is one minus the power (the desired power is 80%), p_c is in this case the probability of success in the methotrexate group (we estimate this at 0.4), p_i is the probability of success in the mycophenolate mofetil group (we estimate this at 0.6), and $\bar{p}$ is $\frac{1}{2}(p_i+p_c)$. We assume 10% will be lost to follow-up in the first six months; details are given in the full proposal. This yields approximately 108 patients in each of the two groups, for a total of 2×108=216 subjects.

A power table is provided below as a sensitivity analysis (to show how the detectable effect size changes with varying success rates.

	80% Power		90% Power	
Success rate with Drug A	**Detectable effect size**	**Success rate with Drug B**	**Detectable effect size**	**Success rate with Drug B**
20%	18%	38%	21%	41%
30%	20%	50%	23%	53%
40%	**20%**	**60%**	**23%**	**63%**
50%	20%	70%	22%	72%
60%	19%	79%	21%	81%

Simulation confirms that this method yields adequate sample sizes for the logistic regression (results not shown).

Note that for the final analysis, the critical value will be adjusted slightly because of the interim analysis.

Sample size readjustment

Simulation suggests that a baseline covariate which is associated with the outcome variable could modestly reduce the sample size needed for 80% power (simulation results are available upon request). Sample size readjustment based on baseline predictors will be considered, subject to approval by the DSMB. The guiding principle is (CHMP, Reflection Paper on methodological issues in confirmatory clinical trials planned with an adaptive design, 2007): Analysis methods that control the type I error must be pre-specified. Whenever possible, methods for blinded sample size reassessment that properly control the type I error should be used, especially if the sole aim of the interim analysis is the re-calculation of sample size.

3.4.2 Power for Subgroup Analyses and Other Analyses

Subgroups in Specific Aim 1.

The prespecified subgroup analysis for specific aim 1 is to examine the difference between the methotrexate and mycophenolate mofetil groups within each anatomic location. Using Equation (5), we anticipate having in excess of 80% power to detect a difference of 25% in success rates.

The power for selected secondary outcomes is provided here.

Secondary Outcomes in Specific Aim 1.

1. Twelve-month endpoint for success. We assume an additional loss of 5% between 6 and 12 months (that is, in addition to the 10% already lost to follow-up in the first six months). **We expect approximately 78% power to detect a 20% difference in success rates at the 12-month endpoint.**

2. Time to corticosteroid sparing control of inflammation. For sample size planning, we use the approximate formula given in Friedman et al (2010) for the number in each group:

$$N = \frac{\left(Z_\alpha + Z_\beta\right)^2\left(\phi(\lambda_C)+\phi(\lambda_I)\right)}{\left(\lambda_I - \lambda_C\right)^2}$$

where λ_C is the hazard in the methotrexate group, λ_I is the hazard in the mycophenolate mofetil group, and $\phi(u) = \frac{u^2}{1-e^{-uT}}$

where *T* is the censoring time (6 months). Previous studies suggest a median success time of approximately 3.5 months for mycophenolate mofetil.[12] **Assuming a 10% loss to follow-up, 108 subjects in each group provides 80% power to detect a difference of 2.47 months in the expected difference.** (Note: λ_C is log(2)/3.5 mo. for this calculation.) We assume an alpha of 0.05 (two sided).

3. Change in BSCVA. For sample size planning, we assume a T-test comparing change scores between the two drugs, assuming a standard deviation of the change in visual acuity of 6.5 letters.[13, 14] The sample size of 108 will provide approximately 80% power to detect 2.63 letters of difference in the change score. In other words, **we expect to have 80% power to detect whether mycophenolate mofetil yields 2.63 letters more of improvement than methotrexate, and we will have greater power to detect greater differences.** The power formula is provided in Chow et al and is computationally implemented in R in the function power.t.test (which we used).[15]

4. Quality of life. For a power calculation, we consider the SF-36 questionnaire, which has two scales, the MCS and the PCS. The raw score standard deviation will be assumed to be 8.4 points; we assume a correlation between baseline and six months of 0.6.[16, 17] Assuming that the baseline score will "explain" roughly 36% of the variance allows us to assume a corrected raw score standard deviation of 6.72 in a simplified calculation in which we treat the analysis as a T-test. The same power calculation formula used in (3) above reveals that **our sample size provides approximately 80% power to detect a raw score difference of roughly 2.57 between the two treatment groups.** This difference is roughly comparable to the small difference in scores found between intermediate uveitis patients and the general population[16], a difference we believe to be more than sufficient to detect clinically significant results. Note that the population mean of this score is standardized to 50 on 0 to 100 scale. Similar analyses will be conducted for the vision related quality of life (i.e. NEI-VFQ-25 and the IND-VFQ).

5. Rate of discontinuation. Based on retrospective studies, we expect approximately 13% to discontinue methotrexate due to tolerability and 5% to discontinue due to safety (laboratory abnormalities or other serious adverse events). We expect approximately 4% to discontinue mycophenolate mofetil due to tolerability and 5% to discontinue due to safety.[12, 18-20] For the purpose of the power calculation, we assume 10% loss to follow-up and consider only the comparison of discontinuation due to tolerability. **We use the power formula given in Freedman et al (p. 104) to calculate a power of 61% for this comparison.[3]**

6. Macular edema. Previous studies suggest approximately 38% of individuals with uveitis will manifest macular edema.[21] **We have approximately 80% power to detect a difference of a factor of two in the final proportion of macular edema (19% vs 38%).**

7. *Macular thickness.* **A sample size of 108 (before loss to follow-up) provides approximately 80% power to detect a 65 micron difference between the two treatment groups, assuming a standard deviation of 160 microns in the final macular thickness.**[22] This analysis is quite conservative, since a difference of 100 microns between these two groups is consistent with previous studies. Moreover, adjustment for variance explained by the baseline thickness (i.e. the use of a smaller effective standard deviation) would yield a still higher effective power.[22, 23]

Specific Aim 2.

In the primary comparison of Specific Aim 2, we will estimate the effectiveness of rescue therapy, controlling for treatment group and reason for failure.

The primary analysis is (a) to estimate the probability of success on mycophenolate mofetil following failure of methotrexate, with 95% confidence intervals, and (b) to estimate the probability of success on methotrexate following failure of mycophenolate mofetil, with 95% confidence intervals.

These results will also be reported by reason for failure of the first drug, by categories of (i) failure because of inability to tolerate the first drug, (ii) failure of the first drug to achieve control (efficacy), or (iii) failure due to safety.

One analysis of interest is to compare the success rates in these two groups, and we include the sample size considerations for this analysis below. For two drugs (mycophenolate mofetil and methotrexate), we conduct the sample size planning as follows (denoting two drugs simply as A and B). For treatment group j=0,1 (0 coding drug B rescue in patients failing drug A therapy, 1 coding drug A rescue in patients failing drug B therapy), we expect $n_j = N_0 r_1 (1 - s_j) r_2$ subjects to be available for Specific Aim 2 (where N_0 is the number of subjects randomized to each treatment, r_1 is the retention fraction in Specific Aim 1 (not lost to follow-up in Specific Aim 1), s_j is the expected success fraction for patients for initial treatment j, and r_2 is the retention fraction in Specific Aim 2.

Thus, the number of available patients for Specific Aim 2 are highly dependent on the results from Specific Aim 1. Scientifically, the result of rescue therapy is important regardless of the result in Aim 1. More power will be available for the primary comparison in Specific Aim 2 if treatment in Specific Aim 1 yielded relatively high and similar failure rates for both drugs. However, even if success rates are very different in Aim 1, the descriptive analyses will still provide important information to guide decision-making on second-line treatment.

Here, N_0=108, and r_1 is assumed to be 0.9 (10% loss to follow-up). For planning Specific Aim 2, we assume a success rate of 60% for patients treated with drug A Specific Aim 1, and a success rate of 40% for those treated with drug B. This is a conservative estimate of the difference expected based on retrospective studies[12, 18-20] and consistent with the pilot study. Finally, we are assuming an additional 5% loss to follow-up during Specific Aim 2 (in addition to the 10% already lost), so that r_2=0.95. The results are summarized in the following table, where the number enrolling does not include loss to follow-up, and the "expected complete" column has taken loss to follow-up into account (n_{jk}).

We anticipate the following:

Initial/Second Treatment	Expected Enrollment SA/2	Expected to Complete SA/2
B/A	58.3	55.4
A/B	38.9	36.9

Thus, we expect a total of n_1=58 patients (rounding down) to have failed one first-line therapy to be enrolled in rescue therapy. Similarly, we expect n_0=38 patients to be enrolled in the other rescue regimen.

Previous observational studies suggest a 42% success rate of mycophenolate mofetil in methotrexate-failing patients,.[24] A simple power analysis for comparing these proportions may be found from the formula (see Chao et al, p. 87):[15]

$$1-\beta=\Phi\left(\frac{|p_1-p_0|}{\sqrt{\frac{p_0(1-p_0)}{n_0}+\frac{p_1(1-p_1)}{n_1}}}-z_{\alpha/2}\right)$$

where p_0 is the probability of success with methotrexate rescue following mycophenolate mofetil failure, p_1 the probability of success with mycophenolate mofetil rescue following methotrexate failure, and Φ is the cumulative distribution function of the standard normal distribution. These assumptions yield a power of 0.87 if the rate of success with methotrexate rescue is 0.15. We have approximately 80% power to detect a difference of 17% if the probability of success with mycophenolate mofetil is 0.42.

A power table for sensitivity analysis is provided. We chose selected scenarios of potential interest to show the wide range of scenarios for which we have sufficient power. The main scenario is the first row of the table; in other rows, we varied the number of patients or the success fractions for the first drug used. In particular, the results are not sensitive to the efficacy difference found in Specific Aim 1.

Power Table for Specific Aim 2

Drug A, then Drug B (number)	Drug B, then Drug A (number)	Success probability of Drug B in patients failing Drug A	Success probability of Drug A in patients failing Drug B	Approximate Power
58	38	0.42	0.15	87%
58	38	0.42	0.17	80%
58	38	0.15	0.42	83%
58	76	0.42	0.15	94%
116	38	0.42	0.15	96%
40	40	0.42	0.15	80%
58	38	0.40	0.15	80%

To summarize, the anticipated number of patients from Specific Aim 1 (58 enrolled in in Drug A, and 38 in Drug B) should provide approximately 80% power to detect a difference of 25% between the two groups, assuming a success probability of 42% and a two-tailed alpha of 0.05.

Secondary Outcomes in Specific Aim 2.

1. Confidence intervals for the probability of success will be reported for each rescue group and anatomic location (i.e. Patients receiving methotrexate or mycophenolate mofetil as first treatment versus receiving it as their second, rescue treatment). Note that in the event that there are insufficient numbers of patients available in one arm of Specific Aim 2 (for instance, far fewer patients available for methotrexate rescue than we anticipate), confidence intervals for estimating the proportion of success can still be computed for the anatomic locations in the other arm.
2. We propose, for each rescue group, to conduct logistic regression using success as an outcome, and reason for failure of the first drug as a categorical covariate (safety, efficacy, tolerability). An overall likelihood ratio test for each will be conducted, with an alpha of 0.05/2=0.025.
3. An additional comparison will be undertaken between first-line and rescue patients with both methotrexate and mycophenolate mofetil.
4. Additionally, the same secondary outcomes assessed in Aim 1 will be analyzed using similar methods.

3.5 Missing data and loss to follow-up

Values of the primary study endpoint (treatment success at six months) cannot be analyzed when the individual is lost to follow-up. We distinguish information which is missing because of possible progression of the underlying condition we wish to treat from information which is lost for some other reason. Earlier, we discussed methods for handling missing values for specific

uveitis fields in individuals. The discussion in this section applies only to loss to follow-up or to dropping out of the study. As emphasized in Carpenter & Kenward (2007), "there can be no universal analysis when data are missing". Our purpose is to vary the assumptions as well as the methods, to establish that the estimates of the treatment effect are robust as such assumptions are varied.

Our priority is the preservation of the intent to treat principle. We propose to report the results from all of the following methods:

1. The use of regression-based multiple imputation, based on all observed data for the patient.
2. Use of longitudinal generalized linear mixed effects regression, with visit as a covariate, and including a random effect for each person and for each eye within each person, using all the available measurements on each individual
3. Sensitivity analysis in which missing final outcome values are assigned success or failure, and the analysis conducted conditional on these assignments.
4. Analysis of complete cases only (individuals for which the six month follow-up is available)

However, we are proposing that **method 4 (complete case analysis) be considered the primary outcome**, based on recommendation by the DSMB. All other analyses are to be considered supplementary.

Multiple imputation will be conducted as follows. The following information will be used as regression covariates: (i) age, (ii) gender, (iii) inflammation assessments at all prior time points (anterior cells, vitreous haze, and retinal/choroidal lesions), (iv) steroid dose, (v) anatomic location (by patient, classified as anterior/intermediate or posterior/panuveitis), (vi) anatomic location by history, (vii) maximum steroid dose within the 90 days prior to enrollment, (vii) steroid dose at enrollment prior to randomization or study-related intervention, (ix) country, and (x) site within country. Any additional covariates must be prespecified. A regression model for the missing outcome information will be derived; specifically, a cross-validated procedure to yield the best prediction based on complete subjects will be derived, and ten multiple imputations will be derived from it. The formula in Little and Rubin[25] will be used to derive the overall test statistic. All replications will be recorded and reported.

An alternative method (which we propose to used for sensitivity analysis) is hot deck multiple imputation (with ten replications).[25] Note that treatment assignment would never be missing. For definiteness, we choose the recursive random partitioning hot deck method used in the R package rrp with the default settings (command rrp.impute).

The possibility of data-driven modeling may render multiple imputation of an outcome variable undesirable to many reviewers as a primary outcome. An alternative method is to model the treatment success of person i at visit j, Y_{ij}, using generalized linear mixed models, with covariates being site, country, treatment assignment, country-assignment interaction, visit (1:6), and visit-drug interaction (method 2 above). Note that additional statistical modeling will be reported, in which we (a) omit visit-drug interaction, and/or country assignment interaction, (b) add visit-country interaction, or (c) add age or gender as covariates.

We believe carrying forward last observations to be particularly unhelpful in this study, because all patients are on a prescribed steroid taper. We also believe that differential loss to follow-up of well performing patients on one drug or the other could falsely make the poorer drug appear to give more favorable results, so that the complete case analysis must be interpreted with caution.

3.5.1 Injections

If a patient receives a corticosteroid injection 90 days after enrollment, it is not possible to truly assess the study drug's ability to manage inflammation at the Month 6 visit. Therefore, as a senstivity analysis, the primary outcome for these patients will be considered by the inflammation levels at the time of the injection. If the patient received the injection because of uncontrolled inflammation, the patient will be considered a treatment failure. If the patient met the definition of treatment success at the time of the injection, the patient will be considered a treatment success.

3.6 Pooling across sites

Approximately three-fourths of patients are expected to come from the [redacted] sites, which are in the same hospital network in the geographic region serving the same patient population. [redacted] serve slightly different populations, although we expect fewer cases overall in the U.S. sites.

3.7 Multiple comparisons

An alpha of 0.05 will be used for the primary analysis of Specific Aims 1 and the primary analysis of Specific Aim 2. The prespecified subgroup analyses of Specific Aim 1 will be conducted at an alpha level of 0.05 (as stated above) as well. However, the use of an overall test prior to subgroup analysis protects the overall type I error rate for the primary outcome, a procedure we apply within the analysis of each secondary outcome as well.

3.8 Interim Monitoring

The study will be monitored by a Data Safety Monitoring Committee (DSMC) appointed by the National Eye Institute. There will be one in-person meeting a year and additional phone calls as deemed necessary. The DSMC will be unmasked and received reports with information by treatment arm from the principal statistician.

3.9 Accrual Rate

Based on enrollment rates in previous trials and preliminary data (see proposal for details) we anticipate enrolling 7-8 subjects per month at all sites, for a total enrollment period of 2.5 years. If we conservatively assume we may only accrue 25% fewer subjects per month, then completion of enrollment would occur 3 years and 3 months after the start of the trial.

We will establish monthly recruitment goals for each of the sites, taking into careful consideration local holidays which may cause recruitment rates to drop at certain times of the

year. Careful monitoring of the recruitment process will enable us to determine whether one of our sites may be falling behind in recruitment, precursory to further investigation and intervention. Standard graphs of realized cumulative recruitment together with cumulative recruitment goals for (a) the study as a whole, and (b) for each of the four sites will be prepared, and provided to the Data and Safety Monitoring Committee at each meeting (or more frequently, if requested).

3.10 Interim Analysis

We propose to conduct two interim analyses, at approximately one-third and at approximately two-thirds of the way through the study. The exact fractions will be determined by availability of data and timing of DSMB meetings. We plan to examine the primary outcome variable using the same statistical model we plan for the final analysis. A flexible alpha spending function is specified in Section 6.

3.10.1 Stopping rules

Stopping rules for benefit, harm, and futility are discussed in Section 6.2. These rules or guidelines would be determined at the first meeting of the DSMC (see Section 6.2).

3.10.2 Execution of interim analysis

The principal statistician [redacted] will conduct the interim analysis in an unmasked manner, subject to independent statistical review by the DSMC. Quality assurance will be conducted by database manager [redacted].

3.11 Final Analyses

The Primary Aim 1 analysis (and secondary objectives), identified in this Statistical Analysis Plan will be performed when all patients complete their 6 month assessment and the window period is completed. All other analyses will be completed after the 12 month visit for Phase I or 6 month visit for Phase II and window periods are complete.

3.12 Software

The standard software program R version 2.12 or higher (http://www.r-project.org) for the MacIntosh OS X will be used for all descriptive and inferential analyses.

4 Analysis Populations

4.1 Summary

The following analysis populations are planned for this study:

- The **screening population**, which is to include all patients who are screened for participation in the trial.

- The **safety population**, which is to include all patients who receive any amount of planned study medication (mycophenolate mofetil or methotrexate).
- The **intent-to-treat efficacy population**, which is to include all patients who are randomized. This is the primary population for the efficacy analyses.
- The **per-protocol efficacy population**, which is to include all patients in the intent-to-treat efficacy population, excluding patients with any of the following: (a) major protocol deviations, or (b) noncompliance with study medications (less than 50% of the study drug received by self report or pill counts at study visits).

4.2 Major protocol deviations

The incidence of deviations from the inclusion and exclusion criteria will be summarized using counts and percentages, and the treatment groups compared for the overall frequency of deviations using a $2\times N$ Fisher's exact test. Similar deviations will be grouped into general categories of deviations for a more condensed summary. A listing of deviations by participant will also be produced. Any major deviations from the protocol will be listed and/or summarized, including, but not limited to, participants who:

- never received study drug
- were subsequently found to be ineligible for the study
- never returned for a follow-up visit
- have follow-up visits outside the prescribed visit window
- received a corticosteroid injection >90 days after enrollment for macular edema or at any time for inflammation

The number and percentage of randomized participants actually receiving study medication, permanently discontinuing study drug (subdivided by reason), and receiving injections >90 days past enrollment will be summarized. A summary of study participants randomized by site will also be provided. Treatment groups will be compared for the proportion and reason for study drug discontinuation using the chi-square test. A summary of participant status at the end of the study period will also be generated with categories including lost to follow-up.

5 Data Collection and Quality Assurance

5.1 Quality assurance and security

Data collection forms, training, security, and quality assurance are discussed in the Manual of Operations for the FAST Treatment Trial.

5.2 Analysis sets

Data sets for analysis will be produced at the [redacted] central site by database manager [redacted] Each will be a Microsoft Excel® worksheet containing a single header line whose variable names match the Access database. Each analysis set will be in the form of a rectangular table in which

each column corresponds to a single variable and each row to an observation. All missing values will be coded explicitly using the string NA (as used in the R software). Codes for categorical variables (such as 1 for male, and 2 for female) will be avoided in favor of self-documenting character strings (such as Male, Female) whenever possible. Automated checks will be made to ensure consistency and that each variable in the analysis set has in-range values (protecting against negative ages, spelling errors in categorical factors, and similar errors).

A detailed codebook will be prepared, containing for each variable, (a) the form from which the variable derived, (b) the text of the question, (c) all possible values for the variable, and (d) summary statistics for the variable. Note that all codes and character strings that represent categorical factors will be clearly defined in the codebook. Units for each continuous variable (e.g. central subfield thickness, logMAR) will be unambiguously indicated for each variable. Each release of the analysis set will be accompanied by the corresponding version of the codebook. Version numbering with dates will be strictly observed. Standard report-generation software included with the R statistical and data analysis package will be used to ensure consistency of the codebook and analysis set at all times.

5.3 Data monitoring reports

Data monitoring reports will be prepared based on analysis data sets. These will be prepared using report-generation software. Monitoring reports will include (a) recruitment reports for each site, (b) compliance reports, (c) retention reports, and (d) data quality reports. These will be reviewed at the central site on a monthly basis, and communicated to the study sites on a monthly basis.

6 Human Subjects

6.1 Summary of final dispositions

All subjects who provide informed consent will be accounted for in this study. The frequency of subjects in each population will be presented. We will also present the frequency of subjects in each subgroup, the frequency of withdrawal and loss to follow-up, and any major protocol violations.

6.2 Data and Safety Monitoring Committee

6.2.1 Scope

A Data and Safety Monitoring Committee (DSMC) will be empaneled by the NEI. We propose that this committee consist of 5-7 individuals, and should include (a) uveitis specialists, (b) an independent biostatistician, (c) a bioethicist, and (d) a member to protect the interest of the Indian population. The committee will meet in person at least once per year. *Ad hoc* meetings as needed may also be convened. All study protocols will be subject to review and approval by Institutional Review Boards at [redacted], and by the DSMC.

The Data and Safety Monitoring Committee will meet to review the interim efficacy data when primary outcome data are available on approximately one third of the study subjects—approximately 6 months after the 72nd subject has been enrolled in the trial (as discussed above in Section 3.10), and when data are available on approximately 2/3 of subjects. The DSMC will make one of the following recommendations:

- Continue the trial without modifications
- Continue the trial with study modifications
- Terminate enrollment or treatment in the trial because of safety concerns
- Terminate enrollment or treatment in the trial because of efficacy

6.2.2 Meetings

All in-person and teleconference meetings of the DSMC and study personnel will consist of (a) "open" sessions, which may be attended as needed by masked study personnel, and (b) "closed" sessions, which may only be attended by unmasked study personnel [redacted] and (c) "closed" sessions attended only by the DSMC personnel. Care will be taken so that *no* treatment assignments, data which would allow treatment assignments to be determined, or outcome data based on treatment assignments will be revealed during the open sessions.

The DSMC will be unmasked. Closed reports will tabulate baseline covariates, adverse events, and outcomes by treatment assignment and study site. Written closed reports will always use the labels Treatment A and Treatment B for increased information security. However, the DSMC will know which drug corresponds to which label.

Interim reports for the DSMC will be prepared by the central [redacted] These reports will include (a) recruitment overall, and by study site, (b) compliance, and (c) retention. The reports will also list study outcomes, and all adverse outcomes, including deaths. The DSMC will determine the database closure dates for each report in advance; archival copies of the (a) main REDCap database, and (b) study analysis file as they exist at the time of each report will be maintained.

All reports will be sent using secure email to the members of the DSMC two weeks prior to each meeting (or more, if desired by the DSMC).

Each printed (hard copy) interim report will be labeled clearly as confidential, bound so that the contents are not visible from the outside, and labeled with the name of each person authorized to receive it. Reports will be kept in possession of [redacted] and only delivered in person or by encrypted email; reports not delivered due to absences are to be shredded. In addition, redacted versions of the interim reports will be prepared which contain no masked study information, and which are suitable for restricted distribution to other personnel on an as-needed basis. All hard copies will be destroyed at the end of each meeting, except for a copy to be kept in a locked file cabinet accessible only to [redacted]

6.2.3 Decisions

The DSMC will make decisions with the benefit of prespecified decision guidelines. These guidelines will be agreed upon at the initial meeting, and are expected to include (a) safety, (b) efficacy, (c) clinical importance, (d) effect of baseline covariates, or (e) validity.

Benefits. Unmasked interim analyses (See Section 3.10) will be conducted to determine whether or not sufficient evidence has accumulated to justify stopping the trial because one treatment is clearly superior (and therefore should be extended to all future cases). The guidelines for efficacy will use group sequential boundaries for judging the statistical significance of the primary outcome measure. The Lan and DeMets flexible alpha spending approach will be used.

Early discontinuation in this trial has the following disadvantages. First, early discontinuation will make it more difficult to assess homogeneity of study sites. In this trial, where the majority of planned enrollment is not from the US, discontinuation at time t=1/3 for instance would occur when only 15 American patients had been enrolled (under our enrollment projections), and at t=2/3, only 30 American patients. Reflection on these small numbers of American patients may limit the adoption of the results of the trial. Second, early discontinuation reduces the power to assess the secondary aims of Specific Aim 1, and for Specific Aim 2. For these reasons, we propose to use conservative stopping rules.

We propose to use a Hwang-Shih-deCani alpha spending function of the form

$$\alpha^*(t) = \frac{\alpha\left(1-e^{-\gamma t}\right)}{1-e^{-\gamma}}$$

with γ chosen to be equal to -5.623626 exactly. This value was chosen to make the alpha at t=1/3 approximately equal to 0.001. The resulting alpha at t=2/3 is approximately 0.0075. The R package `gsDesign` (v. 2.7-04 or higher) will be used for selected analyses.

The proposed plan is to have two interim looks, at approximately t=1/3 and t=2/3 (one third and two-thirds through the study), with the specific fractions to depend on the total available data at face to face DSMB meetings.

The use of a flexible alpha-spending function protects the 0.05 alpha level of the overall trial while allowing for additional interim analyses for efficacy (if needed), without specifying the number and timing of the analyses at the start of the study. We note that the alpha spending function, including the value of γ, cannot be changed once the trial has begun.

Harm. Stopping for harm will be done at the judgment of the DSMC. Several endpoints will be examined, including serious adverse events such as significant and sustained laboratory abnormalities as described in the protocol, or mortality. While the analysis would consider maldistribution of predictive factors such as age, it is recognized that ethical considerations require careful considerations of statistical tests as well as qualitative judgments in the light of experience. Any additional analyses required by the DSMC will be conducted by [redacted], as needed.

Note that serious adverse events (SAE) are reported directly to the medical monitor [redacted] within 24 hours of the time the study site learns of them, and the medical monitor will subsequently pass this information on to the DSMC Chair. The medical monitor will receive

notification of the event, the timing of the event, a medical narrative from the study site, the site location, and the patient identification number. The statistician will report the study treatment assignment to the DSMC Chair if deemed necessary by the DSMC. If use of either drug use clearly results in an unacceptable increase in the risk of treatment failures, then the study will be stopped. It is difficult to fully prescribe boundaries for monitoring safety because there need not be strong evidence to discontinue the study if it appears that the treatment is harmful.

Futility. Early discontinuation due to the unlikeliness of significant findings conditional on interim results would prevent the analysis of Specific Aim 2 and of the secondary aims of Specific Aim 1. No stopping rules based on futility or conditional power calculations are included in the trial plan.

7 Safety and tolerability

The analysis of safety in this study will include summaries of the following:

- Exposure
- Adverse events
    - Adverse events and serious adverse events (including deaths)
    - Adverse events leading to withdrawal
    - Any deaths

7.1 Exposure

Individuals are assumed to have exposure to the drug corresponding to the arm to which they were randomized.

7.2 Adverse Events

7.2.1 Individual events

Adverse event reporting procedures are described fully in the MOP. Non-serious adverse events (not requiring narrative form) are described in the MOP (Section 6.1). Serious non-ocular or ocular adverse events (which must be reported within 24 hours and which require a narrative form) are described in the MOP (Section 6.2). Adverse events will be reported in all presentations and publications according to Consort guidelines.

The proportion of subjects with safety-related events will be compared using logistic regression, using treatment assignment and age as predictors, and including enrollment site as a random effect. Descriptive tables of the number and frequency of adverse events will be broken down by treatment arm, age, gender, and known comorbidities. We will report total adverse events and serious adverse events, cross-tabulated by whether the adverse events were anticipated or unanticipated and by whether or not the adverse event led to discontinuation of medication.

In addition, we will compare the rate of each of the adverse events during the follow-up period using Poisson regression, which can take into account multiple instances of adverse events within

a single subject. Age will be included as a predictor as well as treatment group, and enrollment site will be included as a random effect.

The additional statistical analysis of adverse events we describe here is undertaken strictly to provide additional insight which may be useful to the DSMC and investigators. Interpretation of such findings must reflect the fact that unanticipated adverse events may occur and that we may have insufficient power to make inferences between the arms when considering rare events. Note that adverse events contribute to the outcome of the trial and specific analyses have been defined earlier.

7.2.2 Pooled adverse events

Adverse events will be analyzed according to four main categories:

- Proportion of subjects with *any ocular adverse event*
- Proportion of subjects with *any serious ocular adverse event*
- Proportion of subjects with *any systemic adverse event*
- Proportion of subjects with *any systemic serious adverse event*

The proportion of subjects with these events will be compared between the arms using Fisher's Exact Test. Poisson or negative binomial regression will be applied to compare the rates of overall adverse events, including recurrent events.

8 Reporting conventions

- All tables and data listings will be presented in landscape orientation, unless presented as part of the text of the final report.
- Figures will be presented in landscape orientation, unless the information is substantially easier to interpret in portrait orientation.
- Direct annotation of figures will be preferred to legends. All figures with more than one variable or item will contain either direct annotation or legends. All annotation will be unambiguously identifiable as such.
- Color will be used in figures only when needed to enhance clarity of communication. All color schemes will be evaluated for visual clarity for individuals with diminished color vision. All color encodings will be identified. Redundant encodings (such as the use of different plot symbols or line dash patterns) will be used in addition to color, so that all figures are interpretable after monochrome reproduction at 100 dots per inch. All dash patterns and line widths will be adequate to be distinguishable after monochrome reproduction at 100 dots per inch. Any distinction between plot symbols (circles, filled circles, diamonds, etc.) will remain clear after monochrome reproduction at 100 dots per inch.
- Fixed width sans serif fonts will be used for all labeling (Helvetica, Arial, or Futura).
- Boldface and italics will not be used unless substantial value is added.

- Decorative fonts and enhancements, including borders and shading, will not be used. Decorative presentation methods, such as ribbon graphs, will never be used.
- All information given in figures will also be presented in summary tables (perhaps only included in an Appendix or in supplementary materials).
- Only standard characters will be used in tables and data listings.
- All titles will be centered. The first title line will be the number of the table, figure, or listing. The second and possibly third lines will be the description of the table, figure, or data listing. The ICH numbering convention will be used for all.
- All footnotes will be left justified and at the page bottom. Footnotes will be used sparingly. Reference footnotes will be complete enough to locate any reference based on the information provided (Author, Journal, Pages, Date, or PubMed accession number).
- Missing values for numeric or character variables will be unambiguously identified as such using the special string NA (not available) in all settings; NA is the standard missing value code for our software. Each figure or table caption in which NA is used will indicate the meaning of NA in that figure or table. The abbreviation NA will never be used for any other purpose.
- All date values will presented in the form DDmmmYYYY format (e.g. 01jan2008), using four digit years. June will be encoded as jne (otherwise jan and jun would differ by only a single character), and July as jly (so that the lowercase letter `l`, easily confused with the digit `1`, will not be adjacent to any numerals).
- All tables, figures, and data listings will have the name of the program and a date/time stamp on the bottom of the output.

9 Abbreviations and acronyms

AES Advanced Encryption Standard
CAS Chemical Abstracts Service
DSMC Data and Safety Monitoring Committee
FAST First-line Antimetabolites as Steroid-sparing Treatment
FIPS Federal Information Processing Standard
ICH International Conference on Harmonization
logMAR log of minimum angle of resolution
MOP Manual of Operations and Procedures
[redacted]
NIST National Institute of Standards and Technology
SAP Statistical Analysis Plan
[redacted]

10 Appendix

All computations will be performed using the standard software package R (`http://www.r-project.org`). Statistician [redacted] has twenty years of experience using R or very similar statistical computing environments (S, S-Plus).

Specification of the random number seed and pseudorandom number algorithm determines the entire randomization assignment (as is the case with any pseudorandom number generation method). Accordingly, the random number seed will be kept confidential, and the seed will be chosen carefully. In particular, easy-to-remember numbers or otherwise meaningful numbers (such as telephone numbers, birthdays, and so forth) are to be scrupulously avoided. The chosen seed will be used to generate the final randomization lists.

A printed copy of the randomization lists for all sites, the computer code used to generate them, and the random number seed will be maintained in a locked vault off site. The random number seed chosen will consist of at least eight digits, and a standard linear feedback shift-register algorithm will be used for pseudorandom number generation.[29]

11 Document Revision History

13 January 2015

2.3.1 Specific Aim 1

- Added secondary analysis: To evaluate a difference in treatment success controlling for vasculitis at baseline, assessed at six months.
- Added secondary analysis: To explore the use of a dynamic process model (such as a Hidden Markov model) to assess differences in control of inflammation.

2.4.1 Stratification between sites

- Updated: Patients will be recruited from nine sites: [redacted] (see Manual of Operations Section 2.2 for details).

2.4.4 Unique patient identifiers

- Updated for correct number of sites: Unique patient identifiers will be generated as follows. The first character will be a number: [redacted]

3.2.2 Planned Analysis of Primary Outcome

- Added non-inferiority analysis with a prespecified non-inferiority limit if the primary outcome is no statistically significant.

3.5.1 Injections (New Section)

- Added section: If a patient receives a corticosteroid injection 90 days after enrollment, it is not possible to truly assess the study drug's ability to manage inflammation at the Month 6 visit. Therefore, as a senstivity analysis, the primary outcome for these patients will be considered by the inflammation levels at the time of the injection. If the patient received the injection because of uncontrolled inflammation, the patient will be considered a treatment failure. If the patient met the definition of treatment success at the time of the injection, the patient will be considered a treatment success.

4.2 Major protocol deviations

- Added: received a corticosteroid injection >90 days after enrollment for macular edema or at any time for inflammation

9 March 2017

2.4.2 Randomization List

- Updated: Starting 18 January 2017, all patients will be randomized using the REDCap database. Coordinators can access only the randomization lists for their site. When patients are enrolled, the ID is logged in REDCap and the system provides the medication assignment. All emergency contacts have access to the REDCap database for their site in case of an emergency when unmasking is needed for patient safety. The REDCap database contains assignments for all previously enrolled patients. All previous randomization lists were deemed void and were destroyed. Each site submitted a certification of destruction form.

2.4.6 Provision of randomization list

- Updated: As of 17 January 2017, all randomization lists are electronic on REDCap. Once a patient is enrolled, the study coordinator logs the patient in the database and the system reveals the drug assignment, written out in full.

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