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#### **MUST Follow-up Study Protocol**

**Long-term Follow-up of Patients Who  
Participated in the Multicenter Uveitis Steroid  
Treatment Trial  
(MUST Trial Follow-up Study)**

**Protocol**

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## **Abstract**

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Uveitis refers to several ocular disorders characterized by intraocular inflammation, which in the aggregate are a major cause of visual loss and blindness in the United States. Intermediate uveitis, posterior uveitis, and panuveitis are generally the more severe forms of uveitis, with the highest risk of vision loss, often requiring long-term systemic treatment. The fluocinolone acetonide intraocular implant and systemic therapy are alternative approaches to gaining long-term control of uveitis. The primary objective of the Multicenter Uveitis Steroid Treatment (MUST) Trial was to compare the efficacy of standardized systemic therapy versus fluocinolone acetonide implant therapy for the treatment of severe cases of non-infectious intermediate uveitis, posterior uveitis or panuveitis. As part of the clinical trial, patients had an unprecedented amount of clinical information collected longitudinally, which provides a starting point to evaluate the long-term outcomes of participants with these severe forms of uveitis. The objectives of the MUST Trial Follow-up Study are to evaluate outcomes of the alternative treatment regimens (regarding visual function, ocular and systemic complications of disease or treatment, activity of inflammation, and quality of life) through at least seven years after randomization, to estimate the risk of relapse of uveitis over time after fluocinolone acetonide implant placement, and to conduct additional outcomes research in this well-documented cohort.

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## 1. Background and rationale

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### 1.1 Uveitis: definition and classification

“Uveitis,” in clinical usage, refers to an array of intraocular inflammatory diseases and can be taken to be synonymous with “intraocular inflammation.” In developed countries such as the United States, the substantial majority of intermediate uveitis and panuveitis cases, and about one-half the posterior uveitis cases presenting for care to uveitis practices,<sup>1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12</sup> are presumed to be “autoimmune,” based on the absence of evidence for infection, and a salutary response to corticosteroid and other anti-inflammatory therapies.

Non-infectious uveitides encompass a variety of specific syndromes, each with specific diagnostic features. However, if such a case is established to be non-infectious, corticosteroids are the mainstay of treatment in most instances, regardless of which specific syndrome is diagnosed.<sup>13, 14</sup> The appropriate treatment approach for these conditions depends on two characterizations: 1) whether the clinical course of the uveitis is episodic and spontaneously remitting (with or without intermittent recurrences) versus chronic; and 2) what the anatomic localization of the inflammation is. The former distinction is determined by observing the clinical course of the disease over time, to determine whether remissions occur. The anatomic localization of inflammation is determined by clinical examination. According to the International Uveitis Study Group method for anatomic classification,<sup>15</sup> as updated by the Standardization of Uveitis Nomenclature Working Group,<sup>16</sup> uveitides may be classified in the following categories: anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis. In anterior uveitis, inflammation affects primarily the anterior segment; in intermediate uveitis, inflammation affects primarily the vitreous/pars plana region, with or without snowbank formation, and with or without mild anterior chamber reaction; in posterior uveitis, the choroid and retina primarily are affected, often with overlying vitritis; and in panuveitis, multiple parts of the eye are affected, typically including significant anterior chamber and vitreous inflammation.

Many cases of anterior uveitis follow the acute-remitting pattern, such as HLA-B27-associated recurrent acute anterior uveitis. However, intermediate uveitis, posterior uveitis, and panuveitis often follow the course of a chronic disease. Although intermediate uveitis is in some cases a mild disease, a substantial proportion of patients with this condition eventually require systemic corticosteroid therapy to adequately control their disease.<sup>17</sup> Clinical experience suggests that most cases of posterior uveitis and panuveitis require chronic, suppressive systemic corticosteroid therapy to control inflammation adequately.



## 1.2 Epidemiology of uveitis

In western countries, the best available published estimates of the prevalence and incidence for uveitis are 69-114.5/100,000<sup>18, 19, 20</sup> and 17-52/100,000/year<sup>18, 21, 22, 23</sup> respectively. These prevalence estimates, applied to the United States population in the year 2000, suggest that between 207,000-343,500 persons currently have uveitis, many with chronic disease. Multiplying the estimated incidence rate by the 2000 United States adult population of approximately 210 million (assuming negligible incidence of uveitis in childhood, constant incidence of uveitis at all adult ages, and average survival of 80 years) suggests that between 1-3% of persons will be affected by uveitis during their lifetimes.

In 1990, uveitis was estimated to be responsible for about 10% of visual impairment in the western world, and approximately 30,000 new cases of legal blindness per year in the United States.<sup>24</sup> In 1978, uveitis was estimated to be the sixth leading cause of both prevalent and incident blindness in the United States, based on Model Reporting Area data from 1970.<sup>25</sup> A review of blind registry data in the United Kingdom found that approximately 10% of cases of blindness were attributable to uveitis [S. Lightman, unpublished data (personal communication to J. Kempen, May 28, 2002)]. Vision loss due to uveitis is likely to have a greater impact per case than vision loss from age-related eye diseases, because uveitis most commonly occurs during early to mid-adulthood, resulting in disability during the working years.<sup>26</sup> In addition, uveitis requires a higher average health professional (and patient) effort per case than many other conditions, with an average of 6 clinic visits per year for chronic cases.<sup>27</sup>

Common causes of vision loss in uveitis include cystoid macular edema (CME), media opacities such as cataract or vitreous debris, focal or diffuse retinal injury, and secondary glaucoma.<sup>28</sup> Because vision loss from cystoid macular edema may worsen with exacerbations of uveitis, and visual improvement may result when treatment for cystoid macular edema or cataract is applied, the visual acuity of patients with severe uveitis tends to fluctuate over time,<sup>29</sup> particularly if control of the uveitis is not consistently maintained. Other complications of uveitis can lead to reversible (e.g., cataract) or irreversible (e.g., macular scarring) vision loss.

Based on the limited available evidence and on clinical experience, the risk of visual impairment and blindness attributed to uveitis is high for patients with intermediate uveitis, posterior uveitis, or panuveitis, even those managed at specialty uveitis centers. The retrospective study from two Dutch uveitis referral centers in the early 1990s made the following observations: 1) 48% of patients with intermediate uveitis, posterior uveitis, or panuveitis suffered vision loss to a level of 20/60 or worse within a median observation of 4.3 years; 2) CME was the most common structural complication observed, occurring in 40% of patients with intermediate uveitis, posterior uveitis, or panuveitis and was responsible for the plurality of vision loss (41%) among all patients with uveitis; and 3) vision loss was less frequent in patients with anterior uveitis (19%) than in those with intermediate uveitis (28%), posterior uveitis (46%), or panuveitis (59%).<sup>30</sup> In the MUST Trial at baseline, visual loss to worse than 20/40 (visual impairment) was present in 50% of eyes with intermediate uveitis, posterior uveitis, or panuveitis among patients enrolled in this trial and to 20/200 (legal blindness) or worse in 15% of eyes. In an analysis based on patients, 31% of patients had a visual acuity of worse than 20/40 in their better eye, and 5% of patients had a visual acuity of worse than 20/200 in their better

eye.<sup>31</sup> These data confirm that substantial visual impairment is encountered among patients with more severe types of uveitis.

### **1.3 Standard treatment of uveitis**

Although anterior uveitis often is responsive to topical corticosteroid therapy, the poor penetration of eyedrops into the posterior segment of the eye makes this approach inappropriate as the primary treatment for intermediate uveitis, posterior uveitis, and panuveitis, except in rare instances. Periocular injection of long-acting corticosteroid preparations is a convenient and often effective approach to controlling inflammation in the posterior segment,<sup>32</sup> particularly when either a limited duration of therapy or adjunctive therapy is desired. However for chronic disease, the treating clinician relying solely upon this approach has difficulty predicting when therapeutic benefit from the injected corticosteroid depot may wane, making it difficult to avoid intermittent exacerbations of the inflammatory disease, each with the potential to cause vision loss. Therefore, oral corticosteroids are the mainstay of therapy for chronic, vision-threatening, non-infectious intermediate uveitis, posterior uveitis, and panuveitis. Even for intermediate uveitis, often a less severe disease than posterior uveitis or panuveitis, approximately 50% of patients ultimately will require oral corticosteroids.<sup>17</sup>

Oral corticosteroid therapy has potential side effects. The side effects of short-term therapy, even at high doses, are reversible, relatively mild, and typically well-tolerated (e.g., insomnia, mood swings, Cushingoid facies). However, long-term therapy with doses higher than 10-15 mg/day of prednisone incurs the risk of more substantial side effects, including hyperglycemia, hypertension, hyperlipidemia, osteoporosis, and (in children) growth retardation. Therefore, in cases of chronic uveitis that require long-term administration of oral corticosteroids at moderate to high dosage in order to maintain control of inflammatory disease, immunosuppressive agents typically are added for their corticosteroid-sparing (and in the case of alkylating agents remittive) effects.<sup>33</sup> In addition, for certain specific uveitis syndromes (e.g., Behçet's disease involving the posterior segment<sup>33</sup> serpiginous choroidopathy<sup>34</sup>), initial immunosuppressive therapy is warranted based on evidence suggesting improved outcomes. The immunosuppressive agents effective for treatment of uveitis that are most commonly used include the antimetabolites azathioprine, methotrexate, and mycophenolate mofetil; the T-cell inhibitors cyclosporine and tacrolimus; and the alkylating agents chlorambucil and cyclophosphamide.<sup>33</sup> Each of these agents, in turn, has the potential to cause different kinds of side effects, requiring monitoring. However, because such side effects typically are reversible, a regimen that is effective in controlling uveitis and tolerable for intermediate- to long-term therapy usually can be determined. Expert panel guidelines for the use of immunosuppressive agents for the management of ocular inflammatory diseases are available.<sup>33</sup>

### **1.4 Fluocinolone acetonide implant therapy for non-infectious uveitis**

Because non-infectious uveitis commonly either is localized to the eye or is the only aspect of a systemic disease requiring systemic therapy, a local therapy approach that accomplishes long-term control of inflammation and avoids systemic side effects would be an appealing prospect. The fluocinolone acetonide implant (0.59 mg, Bausch & Lomb, Inc., Tampa, FL) potentially is such a treatment. It is structurally similar to the ganciclovir implant, but smaller in size, consisting of

fluocinolone acetonide coated in a polyvinyl alcohol and silicone laminate attached to a polyvinyl alcohol strut. In vivo, fluocinolone acetonide filters out into the vitreous cavity through a diffusion port, delivering drug to the vitreous with approximately zero order kinetics (0.3-0.4 µg/day) as long as solid drug remains inside, other than a brief period with a higher rate of drug delivery (0.6 µg/day) in the first month. The version marketed is designed to deliver the medication for 30-36 months, and can be replaced if needed.<sup>35</sup>

In a phase 2/3 clinical trial comparing 0.59 to 2.1 mg versions of the implant,<sup>36</sup> 278 eyes of 278 persons were randomly assigned to receive one of the two versions of the fluocinolone acetonide implant. Patients were selected to have asymmetric disease, and the contralateral eye was treated by withdrawal of therapy until reactivation occurred, followed by best medical judgment (trying to avoid systemic therapy). Only pooled results for both implant dosages are available, although results were similar for the two dosages (Glenn Jaffe, verbal communication, May 2, 2005, ARVO Annual Meeting presentation of these results). Essentially all treated eyes initially obtained complete control of uveitis. During follow-up, reactivation of uveitis occurred at or prior to 2 years after implantation in 12% of study eyes, versus 59.7% in these eyes in the year prior to enrollment, and 50.0% in contralateral eyes at 2 years. Use of systemic, periocular, and topical corticosteroid therapy for treatment of uveitis in implanted eyes was significantly reduced (52.5% vs 12.5%, 68% vs 9.7%, and 35.7% vs 27.8% respectively), whereas use of periocular and topical corticosteroids in contralateral eyes increased significantly. Visual acuity was stabilized or improved in the majority of treated eyes, with 24.3% improving by 3 or more ETDRS lines, compared with 5.3% of contralateral eyes. Nearly all phakic eyes receiving implants developed cataract, with 89.4% undergoing cataract extraction by 2 years, vs. 13.3% of fellow eyes. A substantial number of implanted eyes developed intraocular pressure elevation, with 53.7% receiving eye drops to lower intraocular pressure at the two year time point, vs 14% at enrollment (20.2% in contralateral eyes vs. 10.9% at enrollment). In addition, 30.6% of implanted eyes required filtration surgery, versus 0.4% of contralateral eyes, by two years' follow-up.

In addition, the product label<sup>35</sup> reports that procedural complications from implant surgery can occur, including "cataract fragments in the eye post-op, implant expulsion, injury, mechanical complication of implant, migration of implant, post-op complications, post-op wound complications, and wound dehiscence." Post-operatively, some patients reported symptoms of "reduced visual acuity...blurred vision, abnormal sensation in the eye, eye irritation...pruritis, vitreous floaters...increased tearing...dry eye...photopsia, and eye swelling."

## 1.5 Rationale

Based on observations prior to the MUST Trial, fluocinolone acetonide implant therapy appeared to be a promising treatment for severe cases of uveitis, with potential advantages and disadvantages in comparison with standard systemic therapy. The rationale for the MUST Trial, a comparative effectiveness trial evaluating a new local-treatment paradigm v. the established systemic treatment paradigm as outlined in prior versions of the MUST Trial protocol, was to provide a direct comparison of 0.59 mg fluocinolone acetonide implant therapy to state-of-the-art systemic therapy to determine whether the implant represents an improved treatment approach for severe intermediate, posterior, and panuveitis. The MUST Trial reached the design primary outcome (visual acuity at 2 years' of follow-up) for all participants still under follow-up in December 2010. Specific aims of the MUST Trial were to: 1) compare the visual outcomes of participants with uveitis randomly assigned to treatment with the sustained-release fluocinolone acetonide implant to those of participants assigned to treatment with systemic therapy using oral corticosteroids (and corticosteroid-sparing immunosuppression as indicated); 2) compare the efficacy of the 2 treatment strategies for controlling uveitis and ameliorating/preventing structural complications of uveitis over time; 3) compare the rates of ocular uveitis- and corticosteroid-related complications and of systemic complications between the treatment groups; 4) compare the self-reported QoL between treatment groups.

The manuscript representing the accomplishment of these aims was published on August 16, 2011.<sup>37</sup> Nevertheless, because most of the uveitides in this trial are chronic diseases, questions regarding longer-term outcomes of the two treatment approaches continue to be of interest. Fluocinolone acetonide implants were designed to last 2.5-3 years. As fluocinolone acetonide implants run out of drug, participants in the implant arm may experience progressively less favorable outcomes over longer follow-up, due to relapses, and the need for repeated re-implantation surgery over time. In the published study with the longest follow-up, the median time to relapse was 38 months.<sup>38</sup> On the other hand, better control of inflammation under implant than systemic therapy may lead to better outcomes in the long run. Also, the side effect profile of the alternative treatments may differ with longer follow-up. The risk of local side effects may decline after 2 years, because susceptible participants may develop the problems and receive definitive management during the first two years, whereas the risk of systemic side effects may be cumulative over longer follow-up and over time may become sufficiently different to drive choice of treatment. Further follow-up of the cohort will be able to answer these questions regarding which treatment paradigm is best in the long run, given that nearly all participants still under follow-up have agreed to enroll in such a study and that there has been little crossover after announcement of the study's primary results.

Given the remaining questions about fluocinolone acetonide implant therapy versus systemic therapy, and the time-sensitive opportunity to continue following this cohort of participants (most of whom already have enrolled in the study), we will follow the MUST Trial cohort for up to seven additional years after completion of two years' follow-up on all participants in order to evaluate fluocinolone acetonide implant therapy vs. systemic therapy over longer-term follow-up, in order to determine:

- Whether visual acuity outcomes become clearly more favorable over time with one of the alternative treatments
- Whether the excess risk of local side effects with implant therapy (particularly glaucoma) increases progressively over the years or stabilizes after the first implant.
- Whether long-term systemic therapy results in cumulatively increasing systemic side effects that differ to a clinically important degree over longer follow-up (e.g., hyperlipidemia, hypertension, and diabetes mellitus) or whether the risk of adverse systemic outcomes remains low over time
- Whether quality of life outcomes become markedly more favorable over time with one of the alternative treatments
- Whether control of inflammation remains superior with implant therapy than with systemic therapy over long-term follow-up

Our preliminary data suggest that implant replacement is occurring less frequently than expected. Therefore, another important outcome will be:

- To estimate the time-to-reactivation of uveitis after implant therapy, which will guide clinical expectations regarding the outcome of this therapy, and will allow better assessment of the cost-effectiveness of this approach.

In addition to providing information regarding the primary trial question, additional follow-up of the MUST cohort will provide the opportunity for clinical epidemiological studies regarding the course of uveitis. The MUST cohort is unprecedented in providing a broad array of detailed, prospective, observations of participants with the most severe forms of uveitis followed under a standardized protocol, positioning the study well to carry out such studies in addition to studying the longer-term outcome of the alternative treatments.

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## 2. Objectives and study hypotheses

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### 2.1 Specific aims

1. To evaluate whether fluocinolone acetonide implant therapy or systemic therapy is associated with better outcomes over at least seven years after randomization, with respect to:
  - Visual acuity
  - Local ocular adverse effects of treatment or disease
  - Systemic adverse effects of treatment or disease
  - Quality of life
  - Control of inflammation
2. To estimate the distribution of the time-to-reactivation of uveitis after implant therapy
3. To evaluate the cost-effectiveness of the alternative approaches based on at least seven years' treatment
4. To conduct clinical epidemiological studies regarding the course of uveitis

### 2.2 Study hypotheses

1. Implant therapy will result in better visual acuity than systemic therapy by seven years after randomization
  2. Local complications of therapy or disease will plateau after the first 3 years following randomization
  3. Systemic complications of therapy or disease will be greater in the systemic group by seven years after randomization
  4. Quality of life will be superior in the implant group over time.
  5. Implant therapy will show superior control of inflammation over time.
  6. The median time-to-relapse following implant placement will be greater than 3 years.
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### **3. Design**

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#### **3.1 Overview**

The MUST Trial Follow-up Study is a cohort study of participants who enrolled in the MUST Trial. A similar prospective design to that used in the MUST Trial will be used in the MUST Trial Follow-up Study and, while the data collection schedule has been reduced to collect the minimum data needed to ascertain study objectives, the new data will be comparable to the data obtained during the trial phase. The study will not dictate which uveitis treatment should be used; remaining on the randomly assigned treatment is not required. However, based upon current follow-up information, we expect that 90% of enrolled patients will remain in the MUST Trial Follow-up Study and few will elect to change treatments since most are not experiencing uveitis flares. In keeping with good clinical practice, study ophthalmologists will be encouraged to follow the treatment guidelines used in the MUST Trial.<sup>33, 39, 38</sup> These guidelines, written by uveitis experts, are generally accepted as the standard of care. Participants who participated in the MUST Trial will be re-enrolled into the MUST Trial Follow-up Study at approximately 21 clinical centers. Participants will be followed until death, participant withdrawal, or common study closeout planned for April 2017. Participants will be seen every six to twelve months for data collection. Both ophthalmological and medical data will be collected to evaluate the outcomes of treatment of the uveitis, the complications of the uveitis, and complications of therapy. Selected laboratory data related to the complications of systemic corticosteroid therapy will be collected.

#### **3.2 Enrollment**

Patients who enrolled in the MUST Trial are eligible for the MUST Trial Follow-up Study.

#### **3.3 Data collection schedule**

Study visits will be conducted every six months until the ten year anniversary of randomization, then annually thereafter. The date of randomization into the MUST Trial will continue to be the reference date for all study visits, the target for the anniversary study visit being a multiple of 52 weeks after randomization (i.e., the number of years in the study multiplied by 52 weeks) and the target for the anniversary plus six months visit being six months later. To facilitate transition from a quarterly to a twice yearly then to an annual study visit schedule, the study visit numbering system in place for the MUST Trial will remain in effect but only the odd numbered visits will be conducted (i.e., the anniversary and anniversary + 6 month visits) and the study visit windows for these two visits will be expanded from 3 months to 6 months for semiannual visits and to 12 months after reaching the point of annual follow-up as detailed in the study manual of procedures.

Participants may have more frequent visits and/or laboratory testing performed as indicated for clinical care; however, study forms will not be completed at such visits. Data regarding treatment changes and events occurring between study visits will be collected on an interval medical treatment form at the time of a data collection visit, except as specified in the Manual of Procedures and study Policy and Procedure Memoranda.



**Table 1: Data Collection Schedule (after 10 years' follow-up only Randomization Anniversary visits will be conducted)**

Exam/test	Randomization Anniversary (A)	A+6mo <sup>‡</sup>
Visual acuity	X	X
Tonometry	X	X
Ophthalmic exam and history	X	X
Gonioscopy	X	
Color slit lamp lens images*	X	
Color fundus images	X	X
Optical coherence tomography	X	
Humphrey 24-2 perimetry	X	
Medical history	X	X
Blood pressure	X	X
Height	X	
Weight	X	X
EuroQOL	X	X
SF-36, NEI-VFQ	X	X
Hemoglobin A1c	X	
Fasting lipid analysis	X	
Cancer incidence	X	
Bone densitometry	X <sup>†</sup>	

\* Slit lamp lens images for phakic eyes only

<sup>†</sup> BD once every two years (on two year anniversaries of F09 visit)

<sup>‡</sup>Schedule repeats until the common study closeout

## **4. Treatment guidelines**

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In the MUST Trial Follow-up Study, participants may continue on their current therapy or change to another therapy per their study ophthalmologist's clinical judgment and their own preference. For the purposes of good clinical practice and data compatibility, treatment guidelines used in the original clinical trial protocol are provided, which represent the current best practices advocated by expert panels for local and systemic treatment approaches.<sup>31, 33</sup>

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## **5. Outcomes**

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Outcomes measured in the MUST Trial Follow-up Study are the same as those measured in the MUST Trial and have been chosen to capture the benefits of therapy and the impact of the potential adverse effects that may result from uveitis and/or from its treatment. Because uveitis has the potential to cause ocular complications at different sites within the eye, and because both ocular and systemic side effects of treatment may occur, several outcomes will be assessed. The primary outcome is best-corrected visual acuity because preservation of vision is the primary goal of therapy. Other outcomes to be evaluated pertain to the control of intraocular inflammation, the occurrence of ocular complications of uveitis or of therapy, the occurrence of systemic complications of therapy, and self-reported quality of life. Imaging studies employed (and the representative features evaluated) include: lens photography for phakic eyes (cataract), fundus photography (optic nerve morphology, chorioretinal lesions, vascular occlusions), and optical coherence tomography (OCT) (macular edema, vitreoretinal interface abnormalities, including ERM). Health-related QoL data, include health utility (EuroQol 5-dimension and Visual Analog Scale scores)<sup>40, 41</sup> general health-related QoL (SF-36)<sup>42, 43</sup> and vision-related QoL (the 25-item NEI-VFQ).<sup>44</sup>

### **5.1 Visual function**

#### **5.1.1 Visual acuity**

Best-corrected visual acuity score will be measured at every study visit under standardized lighting conditions by certified study examiners using logarithmic (ETDRS) visual acuity charts, according to the method described by Ferris, et al.<sup>45</sup>. A certified visual acuity examiner will measure visual acuity. Although, change in visual acuity data since baseline is the primary outcome, other summary statistics will be analyzed, such as the proportion with low vision (worse than 20/40) and legal blindness (20/200 or worse) over time, etc. Visual acuity outcomes will be evaluated both from the "by participant" (for the worse eye and for the better eye), and the "by eye" (only eyes with uveitis) perspectives.

#### **5.1.2 Visual field**

Humphrey visual field testing, using the 24-2 SITA-fast protocol, will be performed annually. The Humphrey visual field mean deviation score, used in the clinical practice of uveitis as an indicator of the generalized retinal dysfunction that may occur in retinopathies, will be used. For participants who have a new occurrence of abnormal values, the test will be repeated to verify a true abnormality in order to minimize false positive results. Visual field results also will be an aspect evaluated in glaucoma diagnosis (see below).

## 5.2 Intraocular inflammation

Intraocular inflammation will be assessed at every visit by clinical examination. Indicators of inflammatory status will be based on clinician grading of the presence and extent of anterior chamber cells, anterior vitreous cells, and vitreous haze. Each of these will be graded based on previously published standard ordinal scales (0, 0.5+, 1+, 2+, 3+, 4+),<sup>13, 46, 47</sup> using the scales endorsed by the Standardization of Uveitis Nomenclature Working Group,<sup>16</sup> when applicable.

Uveitis will be judged to be “inactive” when meeting criteria for inactivity according to the Standardization of Uveitis Nomenclature Working Group.<sup>16</sup> The examining clinician also will be asked to grade the uveitis as “active,” or “inactive,” based on her/his own judgment.

Clinical examination data regarding consequences of intraocular inflammation also will be noted at every visit, including anterior chamber flare (using the scale endorsed by the Standardization of Uveitis Nomenclature Working Group<sup>16</sup>) and presence or absence of the following: posterior synechiae, peripheral anterior synechiae, angle closure, preretinal neovascularization, choroidal neovascularization, epiretinal membrane/macular pucker, macular edema, optic nerve swelling, pars plana exudation, and retinal detachment. If present, the extent (in degrees) of posterior synechiae and/or of peripheral anterior synechiae/angle closure, will be recorded.

## 5.3 Retinal morphology

To document the ocular abnormalities of uveitis and its complications, fundus photographs and optical coherence tomography (OCT) scans will be obtained using standardized protocols. Images will be sent to the Reading Center (RC) at the University of Wisconsin – Madison, where they will be graded by trained graders masked to treatment status according to standardized protocols. The grading data will be summarized into analysis variables, and transmitted to the Coordinating Center. The details of these procedures are available in the Reading Center Manual of Procedures.

Measurement of macular edema will be a primary goal of ocular image analysis. The presence versus absence of any macular edema and of cystoid macular edema (CME) will be determined by ocular coherence tomography (OCT) and/or color fundus imaging. When edema is present, the area in disc areas of retinal thickening and of cystoid spaces found on color fundus photographs also will be evaluated. Central macular thickness will be measured by OCT. Thus, measures of all three dimensions of the extent of macular edema will be obtained.

Additional retinal morphology outcomes (with the image from which it will be derived in parentheses) include:

- preretinal neovascularization (color fundus photographs)
- vitreoretinal interface abnormalities (OCT, color fundus photographs)
- retinal detachment (color fundus photographs)
- optic disc edema (color fundus photographs)
- glaucomatous optic disk changes, including enlarged cup to disc ratio (estimated in tenths); notching or thinning of the disc rim; partial disappearance of the rim (in clock hours); disc pallor; and disc hemorrhage (color fundus photographs).

Unless otherwise noted previously, these outcomes will be measured as dichotomous variables (present or absent), and if present, their extent will be graded. The presence of other adverse events captured by retinal imaging also will be noted. As participants may be enrolled who have preexisting or coexisting ocular disease (e.g. age-related maculopathy), the presence of other abnormalities will be noted as well.

## **5.4 Quality of life**

Uveitis is expected to effect quality of life (QoL), both through its impact on vision and through effects systemic therapy may have on general health-related QoL and health utility. In addition, because the effect of vision loss on general well-being is profound, the effect of uveitis on general well-being may be substantial despite primary localization of disease to the eye.

The MUST QoL battery consists of the National Eye Institute Visual Function Questionnaire NEI-VFQ, the Medical Outcomes Study Short Form Health Survey SF-36 and the EuroQol, all of which are available both in English and Spanish. The NEI-VFQ is an instrument designed to be responsive to the effects of eye diseases on QoL, particularly addressing vision-related QoL, based on aspects of visual function and ocular symptoms. The SF-36 is an instrument measuring general health-related QoL, which has been demonstrated to fulfill rigorous validity and reliability standards.<sup>42,43</sup> The EuroQol is a generic health index that is widely used in clinical research to calculate a health utility,<sup>41</sup> which is useful as a summary indicator of a participant's self-perceived general health status, which can be used to compare the impact of uveitis (and its treatment) to the impact of other diseases.

## **5.5 Potential ocular complications of uveitis and of therapy**

### **5.5.1 Elevated intraocular pressure and glaucoma**

Intraocular pressure (IOP) elevation and glaucoma in patients with uveitis may be primary, may result from uveitis-induced scarring of the outflow pathways, or may be corticosteroid-induced. IOP will be measured before gonioscopy and dilation using a Goldmann applanation tonometer or a Tonopen (Mentor Ophthalmics, Norwell, Massachusetts). Two measurements will be taken and if they are not within 2 mm Hg, a third measurement will be taken; the average of the two measures or the median of the three will be used as the final IOP. IOP measurements above 24 mm Hg will be considered elevated, and measurements above 30 mm Hg will be considered highly elevated. Rises in IOP of 10 mm Hg will be considered moderate elevations, and a 15 mm Hg rises will be considered large elevations. Use of IOP-lowering medications will be documented as well at all study visits.

Incident glaucoma will be assessed by review of the data accumulated on each participant to determine if glaucomatous optic nerve damage has occurred, and whether or not it developed or worsened during follow up. Standard approaches to categorizing the visual fields will not be possible in this population as many have visual field loss due to the underlying uveitis. Since in many cases the visual acuity data are not reliable for assessing glaucomatous changes, somewhat stricter standards will be used when grading for glaucoma in this cohort. A glaucoma specialist will make an assessment of definite, probable, possible or no glaucoma for each participant based on review of visual field data and stereo optic nerve photographs when identified by the Reading Center as meeting

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one of the following criteria: (1) CDR difference of 0.3 or greater between eyes at baseline (2) an increase in the CDR of 0.2 or greater since baseline; (3) for subjects with a small optic nerve head, an increase in the CDR of 0.1 or greater since baseline. A second glaucoma specialist will independently assess the visual fields of subjects graded by the first reviewer as positive for glaucoma as well as a subset of eyes graded as non-cases. Disagreements will be openly adjudicated by the two reviewers.

### **5.5.2 Cataract**

The occurrence and progression of cataract will be evaluated based on red reflex photographs and slit lamp photographs, graded by masked graders using an adaptation of the Age-Related Eye Diseases Study cataract grading protocol.<sup>48</sup> Slit lamp images will be obtained and graded from eyes that are phakic only. The occurrence of cataract surgery and of YAG laser capsulotomy or surgical capsulotomy during follow-up will be noted at all study visits.

In non-phakic eyes with an intact posterior capsule, posterior capsule opacification will be graded on an ordinal scale by clinical examination (clear; obscured, not affecting vision; obscured, affecting vision; posterior capsule open).

### **5.5.3 Other ocular complications**

Other ocular complications are expected to be uncommon. The following events will be noted if they occur: 1) retinal detachment; 2) vitreous hemorrhage; 3) endophthalmitis; 4) implant extrusion; 5) implant dislocation. Data on other important ocular complications also will be collected.

## **5.6 Potential systemic complications of therapy**

Systemic therapy with corticosteroids and/or immunosuppressive (corticosteroid-sparing) agents can be associated with adverse systemic side effects; detailed data will be collected at all study visits on the following potential complications.

### **5.6.1 Potential complications of corticosteroid therapy**

#### ***5.6.1.1 Hyperglycemia and diabetes mellitus***

Hemoglobin A1C will be measured annually. Assays will be performed locally at clinical center labs. Applying the thresholds recommended by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (American Diabetes Association [ADA])<sup>49</sup>, hyperglycemia will be diagnosed when A1C is above the normal limits of the assay but less than 6.5%. Diabetic-level hyperglycemia will be diagnosed when A1C is 6.5% or greater. Treatment-induced diabetes mellitus will be diagnosed when a subject who was euglycemic at MUST Trial baseline is: 1) observed to have diabetic-level hyperglycemia during follow-up as defined above; and/or 2) medical records demonstrate that the subject was diagnosed with diabetes mellitus (with or without specification of a

relationship of the occurrence of diabetes mellitus to uveitis treatment) during follow-up; and/or 3) the subject was started on therapy for diabetes mellitus.

#### ***5.6.1.2 Osteoporosis***

Subjects will be screened biennially for osteoporosis using dual emission x-ray absorptiometry (DEXA) scanning of the spine (L2-L4) and of the left femoral neck. Generalizing the World Health Organization Study Group postmenopausal osteoporosis guidelines<sup>50</sup> to the setting of corticosteroid-induced bone loss, following the adaptation of the American College of Rheumatology,<sup>51</sup> osteopenia will be defined as a T score between -1 and -2.49 inclusive at the spine or femoral neck (whichever is worse). Osteoporosis will be defined as a T score of -2.5 or worse at the spine and/or femoral neck. Fracture events, also will be noted when confirmed by medical records.

#### ***5.6.1.3 Hyperlipidemia***

Fasting lipid panels, including total cholesterol (TC), low density lipoprotein-cholesterol (LDL), high density lipoprotein-cholesterol (HDL), and triglyceride (TG) levels, will be obtained annually. Changes in LDL from baseline will be evaluated as the main indicator of treatment effects on hyperlipidemia. Based on the categories of the National Cholesterol Education Program (NCEP) Expert Panel (2001),<sup>52</sup> LDL levels will be ordinarily categorized as follows (in mg/dL): <100; 100-129; 130-159; 160-189; and 190+. The change in ordinal category from baseline will be evaluated as an indicator of the effect of alternative treatments on LDL levels. Comparisons of change in ordinal NCEP category from baseline for the other lipid parameters and quantitative change in all lipid levels from baseline also will be evaluated.

#### ***5.6.1.4 Hypertension***

Blood pressure (BP) measurement will be measured at all study visits, using a random zero mercury column sphygmomanometer (or an appropriate substitute if use of such equipment is unavailable). The average of the two readings taken will be used for both systolic and diastolic BP.<sup>53</sup> Blood pressure “stages” (an ordinal scale) will be evaluated in the same manner as that described for hyperlipidemia above. Based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) recommendations,<sup>54</sup> ordinal categories for systolic BP will be (in mm Hg): <130; 130-139; 140-159; 160-179; 180+. Ordinal categories for diastolic BP will be (in mm Hg): <85; 85-89; 90-99; 100-109; 110+. Quantitative changes in systolic BP, diastolic BP, and mean arterial pressure from baseline also will be evaluated.

#### ***5.6.1.5 Weight and height***

Weight without shoes will be measured at all study visits. Height without shoes will be measured annually to allow calculation of body mass index. Change in weight and in body mass index (in kg/m<sup>2</sup>) from baseline, and maximum values for these variables during follow-up will be evaluated.

#### **5.6.1.6 Other potential systemic complications of corticosteroid therapy**

Other less common potential complications of systemic corticosteroid therapy will be deemed to be present when medical records confirm that a diagnosis has been made. These conditions specifically will include diagnosis of any of the following conditions, when not present at baseline: 1) a systemic infection requiring anti-infectious therapy or hospitalization; 2) an axis I psychiatric disorder<sup>55</sup>; 3) pancreatitis; and 4) ischemic necrosis of bone. Data on other important systemic complications including hospitalizations also will be collected.

### **5.6.2 Potential systemic complications of other immunosuppressive therapy**

Immunosuppressive agents with activity against uveitis include azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MM), cyclosporine (CSA), tacrolimus (TAC), cyclophosphamide (CTX), and chlorambucil (CHL). Each of these agents has a unique spectrum of potential systemic side effects. Side effects associated with these medications that are medically important and expected to occur with detectable frequency for participants using these agents during the study are given below.

#### **5.6.2.1 Bone marrow suppression**

- a) *neutropenia*—which may occur with AZA, MTX, MM, TAC, CTX, and CHL—will be evaluated over time as the proportion having a total WBC count of 2500 cells/ $\mu$ L or fewer, which corresponds to an infectious risk. Change in WBC count from baseline and use of granulocyte stimulatory factors also will be noted;
- b) *thrombocytopenia*—which may occur with AZA, MTX, TAC, CTX, and CHL—will be evaluated over time as the proportion having a platelet count 100,000/ $\mu$ L or fewer. Change from baseline will be noted. Hemorrhagic events, requirement for platelet transfusion or other treatments for thrombocytopenia also will be noted;
- c) *anemia*—which may occur with MTX, CSA, TAC, CTX, and CHL—will be evaluated over time as the proportion having a hemoglobin 10 g/dL or less, a level often considered clinically important. Change from baseline also will be noted. Use of transfusions and of erythropoietin also will be noted;
- d) occurrence of myelodysplasia will be noted if confirmed by medical records.

#### **5.6.2.2 Hepatotoxicity**

Hepatotoxicity—which may occur with AZA, MTX, CSA, and TAC—will be evaluated over time as the proportion with any of the following, verified in medical records: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than two times the upper range of normal confirmed by repeat testing; or discontinuation of an immunosuppressive agent due to hepatotoxicity. Cases of persistent elevation of AST and/or ALT after discontinuation of the offending agent will be noted.



### ***5.6.2.3 Nephrotoxicity***

Nephrotoxicity—which may occur with CSA and TAC—will be evaluated over time as the proportion with: serum creatinine elevated to a level of 1.5 mg/dL or higher; or discontinuation of an immunosuppressive drug for renal toxicity. Persistent renal insufficiency will be noted should it occur.

### ***5.6.2.4 Other systemic complications***

Other potential systemic complications of immunosuppressive therapy will be counted as present when the diagnosis is confirmed by medical records.

## **5.7 Reporting potential complications and other medical events**

There will be not be expedited reporting of events that are considered to be complications of uveitis or uveitis therapy, e.g., cataract formation, IOP elevations, or serious infections or other medical events. However, potential complications of uveitis and therapy and other medical events will be reviewed at each visit and medical records regarding such events will be reviewed to ascertain data related to the severity, duration and treatment for these events.

## **5.8 Mortality**

Mortality is not expected to occur at a high rate in this study, because neither uveitis nor the medications used for its treatment are thought to be associated with substantially increased risk of death. However, mortality will be evaluated. Death will be considered to have occurred when one of the following criteria are met:

- . a death certificate for the participant is obtained
- . the participant is listed as deceased in the Social Security Death Index or the National Death Index
- . notice of death appears in print (e.g., an obituary)
- . relatives or acquaintances testify that the participant has died

Date of death will be ascertained from the source reporting that death has occurred.

## 5.9 Cost-effectiveness

### 5.9.1 Analytic Result

The goal of the cost effectiveness analysis will be to determine if the differences in cost and effectiveness between the local treatment approach with fluocinolone implant therapy and the systemic treatment approach over 7 years' follow-up go in the same direction (i.e. one is more expensive and more effective) or if one treatment is both more effective and less expensive.

In the latter case, the treatment that is more effective and less expensive is referred to as "dominating" the other treatment. From an economic perspective, the treatment that is dominant (i.e. more effective and less expensive) should be recommended for a population, although there may still be medical reasons to consider the treatment that is dominated (i.e. more expensive and less effective) in certain situations, according to best medical judgment. When one treatment is more effective and more expensive, an incremental cost effectiveness ratio must be calculated. This ratio shows the additional cost of achieving an additional benefit. As data for the EuroQol are being collected longitudinally in this study, it will be possible to conduct an analysis using quality adjusted life years (QALYs) as an outcome. In that case, the incremental cost effectiveness ratio demonstrates the amount of money that needs to be spent for each extra quality adjusted life year that the superior treatment yields. The incremental cost effectiveness ratio calculation is the difference in costs divided by the difference in the number of QALYs that results from the two treatments over the time period being described:

$$\frac{\text{Cost(Implant)} - \text{Cost(Systemic)}}{\text{QALYs (Implant)} - \text{QALYS(Systemic)}}$$

### 5.9.2 Effectiveness Measures

#### 5.9.2.1 QALYs

The EuroQol and the SF 36 are instruments that can be used to generate QALYs. The EQ 5D and SF36 questionnaires will be completed at all study visits (approximately every six months). The procedure for calculating QALYs will rely on the often used assumption that there is a linear transition between health utility scores at adjacent observations. If there are missing data between observations (e.g. a study subject has an interview at an annual visit and has the next interview at the next annual visit but misses the 6 month visit in between), we can still assume a linear transition between the utility scores at the two annual visits. However, this relies on an assumption of data being missing at random. Alternative methods will be explored via sensitivity analysis in the analysis phase.

For any study subjects who die, the health utility score will be set at zero for the remainder of the duration of the study. The QALY calculations are more complicated for individuals who are lost to

follow up. However, there are multiple options for imputing or modeling missing data over the time between the end of the person's involvement in the study and the end of the study period for participants who drop out of the study early. These range from simple imputation of the mean or mode (not very satisfactory), to a single hotdeck imputation, to multiple imputation techniques. The multiple imputation techniques are best able to simultaneously take care of the combination of issues involving filling in the missing data and exploring the effects on the variance estimate.<sup>56</sup> We can also explore whether the characteristics of individuals with missing data are systematically different from the characteristics of individuals with no missing data.

### **5.9.2.2 Other Outcomes**

QALYs are useful for an analysis of uveitis treatment as there is a diverse range of ocular and systemic complications discussed in Section 6. Specifically, QALYs can capture overall effects of multiple clinical complications that affect quality of life in different ways. When we use measures other than QALYs, we are limited to a single effectiveness outcome in the cost effectiveness analysis. There is a primary outcome for this study: best corrected visual acuity. We will calculate the dollars spent per visual acuity outcome improvement (taking the methodological limitations into account in interpreting this result) as well as the dollars spent per quality adjusted life year gained..

### **5.9.3 Cost**

There are multiple aspects of the cost of treatment in the two arms of the study that must be included in the cost effectiveness analysis. These can be thought of as the costs of the initial treatment, the costs of follow up treatment directly related to the randomly assigned study arm, the cost of ocular complications, and the cost of systemic complications.

The cost of the initial treatment will be based on the reimbursed amounts for the CPT codes for the treatments and the average wholesale prices for the pharmaceutical products that are used.

The resources for follow up visits and follow up medications that are part of the usual treatment costs will be carefully examined and divided into resources that are part of usual care and resources that are only being used because of the research project. Resources that are only being used because the study should not (and will not) be considered part of the cost in any cost effectiveness analysis.

The prices that will be applied to the resources in order to calculate costs will be determined by the study leadership in consultation with the cost effectiveness specialist, characterizing a usual follow up exam and then determining the price.

The costs of dealing with ocular and systemic complications will be difficult to characterize from only the data in this study as the number of each type of complication is likely to be small. To the maximum degree possible, pre-existing literature will be used to find estimates of the costs of dealing with the different complications. In cases in which there is not a description of the costs in the literature, one of two courses of action will be taken. If there are sufficient numbers of a specific type of complication in the dataset, we will use information available on those study subjects' experience to characterize the costs. Otherwise, we will use an expert panel to estimate the costs.

Finally, we have the costs of adverse events regardless of the specific reasons for the adverse events. Again, to the degree that the costs of similar adverse events have been reported in the literature, we

will assign costs based on the previously reported figures. Otherwise, we will again rely on any data that are available and then proceed to use expert opinion to fill in missing cost data.

We do not plan to use specific billing records for any participants in the study.

#### **5.9.4 Perspective**

The perspective for the analysis will be the health care system costs. We will not try to characterize the indirect costs associated with receiving care for the group of participants in the study.

#### **5.9.5 Discount Rate**

For present value calculations, we will use a 3% discount rate. This discount rate may be important in evaluating future costs of the ocular or systemic complications that may arise in this study but last much longer than the intended follow up.

#### **5.9.6 Inflation**

As the data will be gathered over an extended period of time, it will be necessary to make sure that all of the costs are calculated using prices that are appropriate for the same point in time. As we are primarily interested in the health care system perspective, we will use the medical care price index to adjust costs over time. Alternatively, if we have sufficiently detailed quantity information that needs to be multiplied by prices in order to obtain a cost estimate, we can multiply all quantities throughout the study by prices that are applicable at the close of the study to make all cost calculations based on the same valuation of the dollar.

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## 6. Biostatistics

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### 6.1 Sample size, power and detectable differences

The primary outcome of interest for the MUST Trial Follow-up Study is the change in BCVA from enrollment to 7 years of follow-up. In the original MUST Trial, 87% of the 255 participants had bilateral uveitis (479 eyes with uveitis) and the loss to follow-up rate was approximately 2% per year. Treatment cross-overs were observed at annual rates of approximately 1% (implant to systemic) and 2% (systemic to implant). Given that both treatments are expected to control uveitis, we assume that the majority of individuals will remain on their assigned treatment and that the percentage of drop-outs and crossovers will be similar to that observed during the initial study. For the follow-up study this would translate to a crossover of 10% by year 5 and 16% by year 7. Based upon data from the MUST Trial, the within-person correlation between eyes for change in visual acuity was approximately 0.4. The variance of the estimated difference in change increased over time (2.5, 3.5, and 4.0 at 6 months, 1 year and 2 years respectively). We computed the power under two variance assumptions: the 2 year variance holds constant, the variance increases at half the rate observed between years 1 and 2 (0.25 per year). Table 2 shows the estimated power to detect differences in change in visual acuity for each variance scenario.

**Table 2: Power to detect differences in visual acuity**

% cross-over after 7 years of follow-up	Variance (letters)	Difference in change from BL		
		7.5 letters: Benefit increases by 67% of the current rate	10.0 letters Benefit increases by 103% of the current rate	12.5 letters Benefit increases by 139% of the current rate
To Systemic: 7% To Implant: 14% <sup>a</sup>	4.00	84%	98%	99.9%
	5.25	73%	93%	99.1%
To Systemic: 5% To Implant: 11% <sup>a</sup>	4.00	88%	99%	99.9%
	5.25	79%	96%	99.6%

The power to detect differences in rates of ocular and systemic events also is calculated for a selection of representative outcomes of interest. For systemic events, the detectable rate is computed relative to the observed rate for the implant group during the first two years of follow-up. There is 80% power to detect a HR of 2.33, 4.12, 3.87, and 2.25 for hypertension diagnosis requiring treatment (implant 2-year cumulative percentage [2cp]: 4.6%), hyperlipidemia diagnosis requiring treatment (implant 2cp: 1.1%), diabetes (implant 2cp: 1.0%), and osteoporosis (implant 2cp: 5%), respectively. For glaucoma, the focus was on the risk after two years of follow-up, i.e. did the rate of glaucoma for individuals with implants decline to match that of individuals with systemic therapy or did the rate remain increased in the implant group? There is 80% power to detect a HR of 2.40 for the implant group compared to the systemic group (2cp: 4%).

## 6.2 Statistical analysis

The primary outcome measurement in the MUST Trial Follow-up Study is the change in BCVA from enrollment to 7 years of follow-up. The statistical methods used to analyze the long-term follow-up in the continuation study will be the similar to those outlined in the original MUST Trial.<sup>31</sup> For the MUST Follow-up Study, an observational study, the primary analysis still will be according to the original randomization group; that is Intent to Treat (ITT). Secondary analyses will be based on the treatment received, and the ITT analysis will be used as a point of departure from which a causal analysis based in time-varying covariates and propensity scores to account for selection and dropout effects will be built. The relation between the ITT analysis and the causal modeling will be of interest

in its own right, but our principal focus will be on understanding the long-term trajectories via the analysis of the observational data. All primary analyses will be replicated by at least two different analysts.

As for the trial phase of MUST, evaluation of continuous outcomes over time (such as change in BCVA) and binary outcomes over time (such as normal/abnormal IOP) will use a repeated measures analysis with Gaussian or logit links and accounting for the nested correlations between observations over time and (when applicable) between eyes of the same participant.<sup>57</sup> For short to moderate term follow-up, a saturated mean model, including visit and visit by treatment interaction terms, will be used. An unstructured covariance matrix will be used to model the within-eye repeated measurements augmented by random effects to induce cross-sectional between-eye associations in the clinical trials. However, the unstructured covariance model will not be feasible for the long-term follow-up study, because a large number of parameters need to be estimated. Therefore, we will replace it by a Toeplitz covariance structure or a structure composed of a first-order, auto-regressive process (an AR(1) model) along with a random intercept. These structures allow for correlation to decrease with increasing time-separation.

Evaluation of risk factors for time-to-event outcomes such as incidence of ME, cataracts, IOP elevation or glaucoma, as well as time from ME to remission will be performed using Cox proportional hazards regression as well as parametric time-to-failure models, such as gamma models.<sup>58</sup> Implementation of these models allows for clustering (within participants and within eyes), assessment of recurrent events, and incorporation of time-dependent covariates. When the relevant follow-up time in the analysis reflects the clinical time scale (e.g. time since diagnosis of uveitis), it is necessary to incorporate the prevalent cases (longstanding diagnosis of uveitis) into the analysis. To accommodate the prevalent cases we will use the staggered entry technique<sup>59</sup> which is one method of adjusting for potential survival bias. The analysis compares the event rates among participants with similar duration of disease and then combines over these comparisons. Event rates for multiple recurring events, e.g. the number of adverse events, will be modeled using Poisson regression or Negative Binomial regression<sup>58</sup>, including a random effects term to account for the between eye correlation.

All analyses will be performed both unadjusted and adjusted for potential confounders. Effect modification due to factors such as disease location, systemic disease, gender and race also will be explored when appropriate. Robust standard errors will be computed using statistical program-based approaches when available and a bootstrap with the individual as the sampling unit, when a pre-programmed approach is not available.

The follow-up study focuses on a set of primary research questions and related analyses. However, a large number of comparisons are planned for secondary outcomes and caution is needed in the reporting of interpretation of these results. As recommended by Wang et al.<sup>60</sup>, our primary focus for these outcomes will be on the parameter estimates and confidence intervals rather than p-values. Several methods of adjusting p-values for multiple comparisons exist, however no clear consensus as to the most appropriate method is available and it is difficult if not impossible to quantify the number of comparisons. In general, issuing cautions is sufficient, but for identifiable and related sets of estimates we will do adjustments. We expect that related sets of estimates will have a high positive

correlation, making a Bonferroni correction extremely conservative. Therefore, we will estimate the covariance matrix for these related sets using a bootstrap approach and also estimate the null distribution of the minimum p-values for the multivariate distribution of Z-scores using a global null hypothesis permutation distribution or the multivariate normal cumulative distribution program in R. A variety of sensitivity analyses will be performed in order to determine the potential for bias due to modeling assumptions, missing data, and potential biases (especially for epidemiologic analyses). Transformations (e.g., log) of continuous outcomes will be considered when violations of the Gaussian assumption occur. Multiple imputation and pattern mixture approaches will be used to assess the impact of missing data.<sup>61, 62</sup>

For the principal sensitivity analysis, we will retain all features of the primary analysis other than how missing values for visits beyond the last one with a measured value are handled. As is implicit in the primary analysis where missing data indicators are used (e.g. “.” in SAS, “NA” in R), we will treat all missing values, before the last measured one, as Missing at Random (MAR). We will impute other missing values to generate 10 pseudo-complete records for each such individual by sampling from a joint predictive distribution for the missing data given the observed data.<sup>61, 62</sup> We will use a covariance matrix equal to the estimated covariance matrix from the primary analysis, but will “take control” of the prediction mean. Varying the mean of the predictive distribution allows us to assess the sensitivity of our results to a variety of missing data scenarios. The pattern mixture model approach stratifies participants on their pattern of missing data, estimates stratum-specific parameters and then combines estimates over strata using inverse variance weights. The approach is similar to stratified analysis to adjust for potential confounders and allows for comparison of stratum-specific estimates. We stratify by three patterns: complete data, at least one internal measurement missing, and closeout weight missing (along with any other missingness).<sup>62</sup>

The presence of time-varying confounders that are themselves affected by prior levels of exposure may produce large biases in the estimation of causal effects using standard statistical analyses. A classic example, demonstrated by Cole et al.,<sup>63</sup> shows that adjusting for time-varying CD4+ T cell count can dramatically reduce the estimated benefit of HAART on time to AIDS or death. One potential example in the MUST Trial Follow-up Study would be adjusting for cataract status when estimating the time to vision loss for participants receiving regional steroid treatments, since these treatments are known to cause cataracts. Another example influencing participant based outcomes is utilization of immunological agents with systemic steroid treatments. Marginal structural models can be used to correct both for bias induced by a variable affected by exposure and for bias induced by loss to follow-up.<sup>64</sup> The technique employs time-varying inverse probability weights in the place of standard covariate adjustments. We will explore the presence of time-varying confounding by comparing standard Cox proportional hazards models with marginal structural models.



## **7. Data and safety monitoring**

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A Data and Safety Monitoring Committee will be recruited by the National Eye Institute to serve as the monitoring committee. The monitoring committee will consist of voting members and non-voting members (the Study Officers). Voting members appointed by the National Eye Institute will not be involved in the conduct of the MUST Trial Follow-up Study, and will have no affiliation with the companies involved in the development of the fluocinolone acetonide implant. For each DSMC meeting, data will be summarized by personnel from the CC and presented to the DSMC. The frequency of DSMC meetings will be once per year, initially.

Given that this is now an observational study, performance monitoring will be especially important. Performance monitoring will include protocol deviations and missing data. Clinic performance data will be presented at both DSMC and Steering Committee/Research Group meetings.

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## **8. Participant rights and responsibilities**

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### **8.1 IRB approvals**

This protocol will be submitted to the Institutional Review Board (IRB) of participating centers for review and approval. Clinics may not enroll participants or engage in participant related activities without current approval of the protocol by their governing IRB. All MUST Trial Follow-up Study participants must sign a consent statement and medical record release form as well as HIPAA – compliant privacy practices acknowledgment prior to participation in the study.

### **8.2 Confidentiality of participant data**

Confidentiality of participant data will be maintained in accordance with legal regulations. Protected health information will be kept in a secure place. Name, social security number, address, and other such personal data will be kept solely at the clinical center where the participant receives her/his clinical care. Such information will not be transmitted to the Coordinating Center or to other MUST sites. A dataset limited so as to contain a minimal amount of protected health information—that required to make the data useful for accomplishing the purposes of the MUST Trial Follow-up Study—may be disclosed, as needed, to collaborating MUST sites, the NEI, and the FDA. Consent forms include a statement that representatives of NEI, FDA, the Institutional Review Boards, and Coordinating Center may see identifying information while reviewing study records. Clinically relevant information from the study may be placed in the participant's medical record. Release of protected health information to any other persons or organizations will require additional written consent of the participant affected, except as required by law.

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## **9. Biohazards**

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It is possible that specimens collected during the trial will be contaminated with pathogens. All personnel involved in collecting and handling biologic specimens should follow the relevant precautionary measures as currently recommended by the Centers for Disease Control and Prevention.

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## **10. Appendix**

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### **Protocol Committee**

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John H. Kempen, MD, PhD (Protocol Chair, Vice-Chair) of the MUST Research Group)

Douglas A. Jabs, MD, MBA (Chair of the MUST Research Group)

Janet T. Holbrook, PhD, MPH (Coordinating Center Director)

Michael M. Altaweel, MD (Reading Center Director)

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### **Source Documents**

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MUST Trial Chairman's Office, Coordinating Center, and Reading Center Competitive Renewal grant proposals (2010)

MUST Trial Chairman's Office, Coordinating Center, and Reading Center grant proposals

SOCA Monoclonal Antibody CMV Retinitis Trial (ACTG 294)

Protocol SOCA Ganciclovir-Cidofovir CMV Retinitis Trial (ACTG 350) Protocol

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## Document revision history

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**Substantive revisions to the protocol are included in this document revision history. All revisions are captured in the tracked change versions of the documents available on the MUST website and archived at the Coordinating Center.**

**1. Protocol 1.0 (5 August 2003)**

**2. Protocol 1.1 (2 June 2004)**

**4.0 Treatment plan**

Clarification - 0.5 mg fluocinolone acetonide implant will be used for all patients

**9.2 Confidentiality of patient data**

Added - NEI, FDA, IRBs, CC and B&L might see identifying information

**3. Protocol 1.2 (26 Aug 2004)**

**3.1 Design Overview**

Number of projected clinical centers changed from 19 to 20-40

**3.2 Enrollment and randomization**

Elaborated on permissible use of uveitis therapies at enrollment: Current/past use of oral corticosteroids or *immunosuppressive agents* acceptable...*Previous use of fluocinolone acetonide acceptable if any implant still present in an eye placed more than 3 years previously*

**3.2.1 Inclusion Criteria**

- 1) Changed from 18 to 13 years
- 3) Clarified that uveitis activity needs to be of a degree for which systemic corticosteroid therapy is indicated in the judgment of a MUST-certified ophthalmologist ("severe" uveitis)

**3.2.2 Exclusion criteria**

- 3) Changed exclusion from more than *two* anti-glaucoma medications to more than one in one or more eyes with "severe uveitis"
- 4) New exclusion criterion: advanced glaucomatous optic nerve injury meeting specified criteria

**4. Treatment plan (additions):**

- Prior to rz ophthalmologist identifies surgical procedures currently indicated for each eye
- Oral corticosteroids as option to quiet anterior chamber - not to be used routinely
- Qualification for timing of initial implant surgery- may be done within month of randomization if delay is indicated according to bmj
- Instruction to insert implant into vitreous cavity with cup faced forward
- Simplified criteria for replacing implant to if indicated according to bmj.
- Removed "3 clock hour" as descriptor of conjunctival peritomy.

**4.1 Treatment**

Added: Surgery indicated at enrollment may be performed in combination with implant surgery per bmj but combined vitrectomy surgery to clear vitreous opacities should be avoided

**4.2.1 Oral corticosteroid therapy (additions)**

- Prior to rz ophthalmologist identifies surgical procedures currently indicated for each eye
- Option for initial use of intravenous corticosteroids for uveitis control when indicated
- Clarification that prednisone guidelines apply to alternative corticosteroids at equivalent dose

- Instructions re: starting and chronic maintenance doses of prednisone doses 10 mg or lower judged to be causing unacceptable corticosteroid-related side effects vis a vis starting dose and chronic dose
- Instructions re: using current regimen as starting dose for patients whose uveitis is controlled on oral corticosteroid therapy at randomization

#### **4.2.2 Potent immunosuppressive drugs**

Added: Because of the potential for additive toxicity, use of two agents of the same class (antimetabolite, T-cell inhibitor, or alkylating agent) should be avoided

#### **4.2.2.6 Cyclophosphamide**

Specified dose for trimethoprim /sulfamethoxazole

#### **4.3.6 Ancillary therapy for prevention or treatment of adverse effects of systemic therapy**

Deleted: *Patients who develop osteoporosis will be treated with an antiresorptive agent, such as alendronate.*

### **5. Data collection**

- Added: Study visits not to be conducted within one month of any intraocular surgery
- Revisions to Table 1: MUST Data Collection Schedule:
  - Color slit lamp lens at 6 month s; color fundus photos at 1 and 6 month visits;
  - height at baseline; EuroQol' as replacement for 'QOL'; SF-36 and NEI-VFQ at baseline, and 6 month visits; casual instead of fasting serum glucose added for 3 month visit

### **4. Protocol 2.0 (1 Oct 2004)**

- Added document distribution and revision history sections
- Corrected reference numbers in text and corrected reference list

### **5. Protocol 2.1 (16 Nov 2004)**

#### **6.9 Cost-effectiveness Outcomes -added section**

#### **6.5.2 Cataract**

Revised grading protocol for posterior capsule opacification in pseudophakic eyes with an intact posterior capsule from use of an ordinal scale to classification scheme: clear; obscured, not affecting vision, obscured, affect vision; posterior capsule open

### **6. Protocol 2.2 (1 Apr 2005)**

#### **1.1 Uveitis definition and classification**

Added reference by Standardization of Uveitis Nomenclature (SUN) Working Group

#### **1.2 Epidemiology of uveitis**

Added prevalence and incidence rates per Gritz and Wong, 2004

#### **3.1 [Design] Overview**

Added that study will begin under an IND granted by the FDA (IND #70,211).

#### **4.1 Fluocinolone acetonide implant**

Removed grading specifications for uveitis suppression and reactivation

#### **5. Data Collection, Table 1:**

- Corrected errors: Humphrey perimetry changed to 12 months instead of 15 months
- EuroQOL not collected at 3 months ; changed serum glucose to plasma glucose;
- Casual plasma glucose added at all visits except baseline and annual visits
- Added serum pregnancy test at baseline visit for women who are able to become pregnant
- † note added: The baseline DEXA scan must be completed no later than 2 weeks after randomization

#### **6.1.2 Visual field**

Specified 30-2 SITA-fast protocol



## **6.2 Intraocular inflammation**

Anterior chamber cells, anterior vitreous cells, and vitreous haze, intraocular inflammation, anterior chamber cell and inactive uveitis to be evaluated using SUN Working Group criteria/scales

### **6.5.1 Elevated intraocular pressure and glaucoma**

- Changed protocol to measure IOP from “protocol followed by CIGTS to “a standardized protocol”
- Added : In the case that the two measurements differ by  $\geq 2$  mm Hg, a third measurement will be taken to adjudicate the discrepancy. Removed comment re use of average of 3 Tonopen measurements;
- Changed cutoff for elevated IOP from 21 mm Hg to 24 mm Hg
- Added rises in IOP by 10 mm Hg considered moderate elevations and 15 mm Hg rise considered large elevation; use of IOP-lowering medications will be noted
- Replaced diagnosis of glaucoma with description of how incident glaucoma to be assessed

#### **6.6.1.3 Hyperlipidemia**

Removed fasting lipid panel at 3 months

### **7.1 Sample Size, power and detectable differences**

Added: A difference in the mean change in visual acuity of 15 letters or more will be considered a clinically significant event.

## **7. Protocol 2.3 (16 May 05)**

### **Abstract and throughout:**

Expected life of implant changed from 3.0 years to 2.5 years  
0.5 mg fluocinolone acetonide intraocular implant changed to 0.59mg

### **1.4 Fluocinolone acetonide implant therapy for non-infectious uveitis**

Revised to incorporate data released after FDA approval of implant. References 31 and 32 replaced with product insert and 3 May 05 press release.

### **5. Data Collection**

Correction to first footnote: F6, F7, F8, and F9 data collection tables repeat every 12 months until the common study closeout

#### **6.1.2 Visual Field**

Changed Humphrey visual field protocol from 30-2 to 24-2

## **8. Protocol 2.3 (31 May 05)**

### **5. Data Collection**

Corrected typos in table (gonioscopy, color slit lamp & fundus photos, FA, OCT)

## **9. Protocol 2.4 (30 June 05) (Patient enrollment began under this version)**

### **4.1 Fluocinolone acetonide implant therapy**

Interval between 1<sup>st</sup> and 2<sup>nd</sup> eye surgeries changed from 1 to 2 weeks.

#### **4.2.2.5 Tacrolimus**

Revised dosing and monitoring guidelines

#### **4.2.3 Biologics section added**

### **5. Data collection**

Revised table to include height measurement at annual visit only

## **10. Protocol 3.0 (13 Jan 2006)**

### **1.4 Fluocinolone acetonide implant therapy for non-infectious uveitis**

Changed length of time implant designed to deliver medication from 30 months to 30-36 months.

#### **3.2.1 Inclusion criteria**

3) Time period for meeting active uveitis criterion increased from last 30 days to 60 days

- 5) Vision requirement modified from BCVA better than 20/200 (35 letters) for at least one eye with "severe uveitis" to hand motions or better in at least one eye with uveitis.
- 6) Baseline intraocular pressure of 24 mm Hg or less in all eyes with "severe uveitis" was changed to "all eyes with uveitis"
- 7) Deleted inclusion criteria: Media clarity sufficient to allow visualization and imaging of the fundus in at least one eye with "severe uveitis"; Criteria 8 and 9 renumbered to 7& 8.

### **3.2.2 Exclusion criteria**

- 3) Criterion previously referred to eyes with severe uveitis"; was changed to refer to one or more eyes with uveitis that would receive an implant if randomized to the implant treatment arm

### **4.1 Fluocinolone acetonide implant therapy**

- "Severe uveitis" (defined as uveitis for which systemic corticosteroid therapy is indicated) was replaced with "uveitis for which systemic corticosteroid therapy is indicated".
- Specifications for the anchoring suture changed to a double-armed 8-0 prolene suture; previously protocol specified either double-armed 8-0 or 9-0 prolene suture could be used

### **Reference list**

Updated reference 16, in press at time of last protocol revision, was published

## **11. Protocol 3.1 (29 Nov 2006)**

### **3.2.1 Inclusion criteria**

- 3) Removed specification of: vitreous cells, inflammatory debris, and/or active chorioretinal lesions for active uveitis

## **12. Protocol 3.2 (08 Mar 2007)**

### **3.2.2 Exclusion criteria**

- 3) Deleted glaucoma requiring more than one anti-glaucoma medication in one or more eyes with uveitis

### **6.5.1 Elevated intraocular pressure and glaucoma**

Protocol for IOP measurement with Goldmann applanation tonometer changed from 2 person 'masked' reading to one-person reading

## **13. Protocol 3.3 (08 Jan 2008)**

### **3.1 Design overview**

The number of clinical centers was changed from 21 to 23 clinical centers. The sample size was changed from 400 patients, 200 per treatment group to 250 patients, 125 per treatment group.

### **7.1. Sample size, power and detectable differences**

Revised from 200 to 125 patients in each group; difference in mean change in visual to be detected changed from acuity changed from 15 letters to 1.5 lines

### **9.2 Confidentiality of patient data**

Bausch and Lomb removed from list of entities that may receive a dataset with minimal amount of protected health information and as an entity that may see identifying information during review of study records

## **14. Protocol 3.4 (22 Jan 09)**

### **4.3.2 Periocular corticosteroid therapy**

Circumstances in which periocular injections of corticosteroids permitted as ancillary therapy were modified (italicized text added) *other ancillary treatment of uveitis-associated complications –e.g. for persistent or refractory macular edema in either group.... Periocular corticosteroid injections should not be given repetitively on a routine basis as a primary form of therapy, particularly in the systemic therapy group.*

#### **4.3.3 Intraocular corticosteroid injection**

Revised to permit intraocular injections of corticosteroids as ancillary therapy, only when indicated for the stated circumstances; previously were not included in the treatment protocol except for patients being managed under “best medical judgment”.

### **15. Protocol 4.0 (26 October 2010)**

#### **Global changes**

- Name change from Multicenter Uveitis Steroid Treatment Trial (MUST) to Long-term Follow-up of Patients in the Multicenter Uveitis Steroid Treatment Trial (MUST Trial Follow-up Study)
- Features of randomized trial changed to those of longitudinal cohort study, i.e deleted assigned treatment and treatment protocols
- Outcomes are for medium and long-term follow-up
- References to collecting at baseline or 1 month follow-up visit were deleted
- Changes for clarity, consistency, and style made throughout

#### **Abstract**

Primary objective changed from comparing efficacy of standardized systemic therapy vs fluocinolone acetonide implant therapy to evaluating long-term consequences of the alternative treatment regimens and to conduct broad outcomes research on the well-documented cohort of enrolled patients

#### **Table of contents**

Sections pertinent to randomized trial phase but not follow-up study phase were removed or modified; remaining sections were renumbered accordingly

#### **1.2 Epidemiology of uveitis**

- New references (18-23 and 27) added for prevalence and incidence rates:
- Average clinic visits per year (6) for chronic cases of uveitis added
- Additional information on the risk of visual impairment and blindness attributed to uveitis was added (references 30-31)

#### **1.5 Rationale**

Rationale, specific aims, and study hypotheses were modified to reflect the focus on longer-term outcome assessment at 5 and 8 years of follow-up for continued follow-up of MUST patients after reaching the two year outcome and new references 38-41 were added.

#### **2.1 Specific aims and 2.2 Study hypotheses revised for follow-up study**

#### **3.1 Overview**

Study design changed from a randomized clinical trial to a cohort study; data collection reduced to the minimum required to meet study objectives; study will not dictate uveitis treatment

#### **3.2 Enrollment**

- Deleted: inclusion and exclusion criteria for the MUST Trial
- Added: Patients who enrolled in the MUST Trial are eligible for follow-up study

#### **3.3 Section changed from Randomization to Data Collection Schedule**

Section on randomization no longer applies and was deleted; data collection schedule (previously in section 5) was revised to remove from baseline and 3 month visits.

#### **4. Section name changed from Treatment to Treatment guidelines**

Added: patients may continue on their current therapy or change to another therapy per their study ophthalmologist’s clinical judgment and their own preference. For the purposes of good clinical practice and data compatibility, treatment guidelines that conform to current best practices advocated by expert panels and original clinical trial protocol are provided for local and systemic treatment approaches.

## **6. Outcomes**

- Added: listing of imaging studies employed and representative features evaluated
- Deleted: information on masked procedures

### **6.1.2 Visual field**

- Added: Test will be repeated if there is a new occurrence of abnormal values
- Added: Standard approaches to categorizing the visual fields will not be possible in this population as many have visual field loss due to the underlying uveitis
- Added details about the reviews by two independent reviewers to diagnose definite, probable, possible, or no glaucoma

### **6.2 Intracocular inflammation**

- Deleted: For uveitic conditions, such as serpiginous or birdshot retinochoroidopathy, in which inflammation may be limited to the choroid and retina, clinical judgment of activity will be substituted for an activity grading based on anterior chamber cells and vitreous haze.
- Deleted: If present, . . . the extent (in disc areas) of preretinal neovascularization and of choroidal neovascularization, will be recorded. The relationship of inflammation activity to ocular surgery will be evaluated at the time of statistical analysis. Because study visits (other than the first follow-up visit after randomization) will take place at least one month after ocular surgery, post-operative inflammation is unlikely to confound grading to inflammation substantially.

### **6.3 Retinal morphology**

- Deleted: indices of macular edema are expected to be strongly related to reduced visual acuity

#### **6.5.1 Elevated intraocular pressure and glaucoma**

Clarified that when the first two IOP measurements are not within 2 mm Hg, a third measurement will be taken; the average of the two measures or the median of the three will be used as the final IOP

#### **6.5.2 Cataract**

Deleted : Occurrence also will be graded clinically at each study visit using standardized grading system.

##### **6.6.1.1 Hyperglycemia and diabetes mellitus**

Deleted: . Description of ordinal scale to be used to evaluate difficulty controlling diabetes mellitus

##### **6.6.1.2 Osteoporosis**

Deleted: Fracture events are likely to be infrequent during the follow-up period of the trial

### **6.8 Adverse event reporting**

Deleted: CC will send copies of all SAEs to Bausch & Lomb, Inc. within 7 working days of their receipt at CC and will distribute reports of SAEs from one center to all other centers

### **7.1 Sample size, power and detectable differences**

Entire section replaced for follow-up study

### **7.2 Section header changed from **Principles for data analysis will include** to **Statistical analysis****

Entire section replaced for follow-up study

## **8. Data and Safety Monitoring**

- Deleted :Treatment effects monitoring, including formal interim analyses, will be conducted by DSMC
- Deleted: The primary focus of these analyses will be on comparisons of the treatment groups with respect to the safety and efficacy measures. The DSMC will not be masked.
- Added: monitoring will focus on occurrence of side-effects of treatments and performance

## **16. 4.1 (04 Jan 2011)**

### **3.1 Overview**

- The data collection schedule refined to collect the minimum data needed to ascertain study objectives but new data will be comparable to data obtained during the trial phase.
- Frequency of visits for data collection changed from every 3 months to every 6 months

### **3.3 Data collection Schedule**

- Information added re: study visit timing study visit naming conventions (odd vs even study visits) and study visit windows in light of moving from study visits every 3 months to every 6 months
- Change in frequency of bone densitometry (BD) from every year to every two years
- BD collection changed from annual to every 2 years (on two year anniversaries of F09 visit)
- Slit lamp images for phakic eyes only; previously slit lamp images for all eyes
- Fluorescein angiography deleted
- Complete blood count at annual visit deleted
- Chemistry panel at annual visit deleted
- Casual plasma glucose at non-annual visits deleted
- Fasting plasma glucose at annual visits replaced by Hemoglobin A1C

### **4.0 Treatment guidelines**

Added: The choices for another therapy will be limited to those therapies licensed/approved for use by the clinical center's national regulatory agency. At present the fluocinolone acetonide implant is not approved for use in Australia or the United Kingdom and thus will not be a treatment option for patients who were randomized to systemic therapy in the trial phase. The study will continue to provide implants for patients who were randomized to implant in the trial phase.

### **5. Data collection**

Section deleted; information was moved to section 3.3 and subsequent sections re-numbered

### **5. Outcomes**

- Deleted: The adverse events reporting system currently in use for the MUST Trial will be continued to ascertain the occurrence of both anticipated and unanticipated adverse events. When indicated, patients suffering adverse events will be referred for appropriate ophthalmic or medical care.

#### **5.5.3 Other ocular complications**

- Deleted: Additional serious adverse ocular events will be noted through adverse events reporting system.

#### **5.6.1.1 Hyperglycemia and diabetes mellitus**

- Annual measurement of hemoglobin A1C replaced fasting plasma glucose for diagnosis of diabetic-level hyperglycemia (6.5% or greater); reference #52 replaced

### **5.8 Adverse event reporting replaced with Section 6.8 Complications of therapy**

### **7.0 Data and Safety Monitoring Committee**

- Section modified for follow-up study. Monitoring for trial phase was focused on occurrence of side-effects of treatments and adverse events; in follow-up study DSMC's evaluation of complications of treatments will focus on long-term trends in the occurrence of significant clinical events including rate of IOP lowering surgeries, incidence of glaucoma, osteoporosis, serious infection, diabetes, and hyperlipidemia.

## **17. 4.2 (1 November 2011)**

### **Global**

Changed study period from 6 additional years of follow-up (a total of 8 years of follow-up) to 5 additional years of follow-up (a total of 7 years of follow-up)

### **Abstract**

Added specifications of outcomes: regarding visual function, ocular and systemic complications of disease or treatment, activity of inflammation, and quality of life) through seven years after randomization, to estimate the risk of relapse of uveitis over time after fluocinolone acetonide implant placement

### **1.4 Fluocinolone acetonide implant therapy for non-infectious uveitis**

Deleted safety data from phase 1/2 studies

### **1.5 Rationale**

Added

- Manuscript representing the accomplishment of the specific aims of the MUST Trial was published on August 16, 2011 [online ahead of print].
- Nearly all patients who were still under follow-up agreed to participate in the follow-up study and that there has been little crossover after announcement of the study's primary results.
- Added bulleted list of specific aims:
  - To determine whether visual acuity outcomes become clearly more favorable over time with one of the alternative treatments
  - To determine whether the excess risk of local side effects with implant therapy (particularly glaucoma) increases progressively over the years or stabilizes after the first implant.
  - To determine whether long-term systemic therapy results in cumulatively increasing systemic side effects that differ to a clinically important degree over longer follow-up (e.g., hyperlipidemia, hypertension, and diabetes mellitus) or whether the risk of adverse systemic outcomes remains low over time
  - To determine whether r quality of life outcomes become markedly more favorable over time with one of the alternative treatments
  - To determine whether control of inflammation remains superior with implant therapy than with systemic therapy over long-term follow-up
  - To estimate the time-to-reactivation of uveitis after implant therapy, which will guide clinical expectations regarding the outcome of this therapy, and will allow better assessment of the cost-effectiveness of this approach.

### **2.1 Specific aims of the MUST Trial Follow-up Study**

Added detail to specific aims as was added in section 1.5 Rationale

## 2.2 Study hypotheses

Replaced:

1. Participants who consistently have control of inflammation will have better visual outcomes than ones who do not.
2. Remission of inflammation (defined as sustained inactive disease after treatment is discontinued) will occur in a minority of participants; predictive “risk factors” for remission can be identified.
3. The majority of participants initially controlled with each treatment will continue to be controlled by the same treatment regimen over time.
4. Complication rates in each treatment arm will plateau over time (participants will tend to have or not have adverse events), with most adverse events occurring in the first 2 years.
5. Visual acuity, control of inflammation, and occurrence of side effects will predict QoL.
6. Long-term therapy with low-dose oral corticosteroids (<7.5 mg/day prednisone) is safe with respect to the side effects measured in the study.

With

1. Implant therapy will result in better visual acuity than systemic therapy by seven years after randomization.
2. Local complications of therapy or disease will plateau after the first 3 years following randomization
3. Systemic complications of therapy or disease will be greater in the systemic group by seven years after randomization
4. Quality of life will be superior in the implant group over time.
5. Implant therapy will show superior control of inflammation over time.
6. The median time-to-relapse following implant placement will be greater than 3 years.

## 3.1 Overview

Updated with information about participants continuing follow-up after being informed of 2 year results

## 5.2 Intraocular inflammation

Corrected typo (trace changed to 0.5+) in description of ordinal scale for grading anterior chamber and anterior vitreous cells

### 5.5.1 Elevated intraocular pressure and glaucoma

The methods for assessment of incident glaucoma were revised. Cup to disc ratio cutpoint criteria for glaucomatous change were removed. The role of second glaucoma specialist was clarified. The second glaucoma specialist will independently assess the visual fields of subjects graded by the first reviewer as positive for glaucoma as well as a subset of eyes graded as non-cases. As previously written the reader would have assumed the second glaucoma specialist would review the data for all participants.

## 5.7 and 5.8

Switched the order of these sections and renamed section 5.7 Reporting potential complications and other medical events

## **6.0 Biostatistics**

Section updated with power calculations for detecting differences in change in BCVA and differences in rates of ocular and systemic events at 7 years of follow-up

## **7.0 Data and Safety Monitoring**

Deleted information that the DSMC currently in place for the MUST Trial will continue and added that the monitoring committee will be recruited by the National Eye Institute.

## **Appendix**

### **Protocol Committee**

Ordering of membership rearranged to list Protocol Chair first.

### **Source Documents**

Added back the original 3 source documents that were included in earlier versions of the protocol

### **Document History**

Section streamlined to provide summary of changes detailing only the critical revisions

## **References**

Added reference 38; deleted the following references and renumbered remaining references

40. Golstein DA, Godfrey DG, Hall A, Callanan DG, Jaffe GJ, Pearson PA, Usner DW, Comstock TL. Intraocular pressure in patient with uveitis treated with fluocinolone acetonide implants. *Arch Ophthalmol* 2007;125(11):1478-85. PMC ID: 17923537.
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## **18. 4.3 (6 September 2012)**

### **2.1 Specific aims**

Defined control of inflammation as grade 0 anterior chamber cells, grade 0 vitreous cells and inactive chorioretinal lesions

### **3.3 Data collection schedule, Table 1**

Added Color fundus images at 6 month visits

#### **5.1.1 Visual acuity**

Visual acuity examiner is no longer required to be masked to participant's treatment for uveitis; removed "masked" as descriptor of certified visual acuity examiner

## **19. 4.3 (24 October 2012)**

### **2.1 Specific aims**

Removed specifications/description of control of inflammation, i.e., grade 0 anterior chamber cells, grade 0 vitreous cells and inactive chorioretinal lesions)



## **20. Version 4.4 (16 July 2015)**

### **Abstract**

Clarified that follow-up will be for “at least” seven years.

### **1.5: Rationale**

Deleted mention to 7 years after randomization as a parenthesis regarding the duration of “longer-term” follow-up

Changed the additional follow-up from “five” to “up to seven” additional years after completion of two years’ follow-up on all participants

### **2.1: Specific Aims**

Clarified duration of follow-up will be “at least” seven years.

### **3.1: Overview**

Number of clinical centers was updated to approximately 21

Date provided for common study closeout: April 2017.

Frequency of visits updated to “every six to twelve months.”

### **3.3: Data collection schedule**

Updated to reflect annual study visits after reaching the ten year anniversary of enrollment, and 6-month wide visit windows beginning at that point.

The possibility that data would be collected between study visits “as specified in the Manual of Procedures and study Policy and Procedure Memoranda” was enunciated.

Data collection table updated for change to annual visits only after 10 years’ follow-up

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