Supplementary Online Content 2


MUST Protocol and Statistical Analysis Plan
Multicenter Uveitis Steroid Treatment (MUST) Trial Protocol

Version 2.4

30 June 2005
Document distribution

<table>
<thead>
<tr>
<th>Version</th>
<th>Version date</th>
<th>Distribution</th>
<th>Distribution Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>5 August 03</td>
<td>CHR</td>
<td>7 April 04</td>
</tr>
<tr>
<td>1.1</td>
<td>2 June 04</td>
<td>CHR</td>
<td>7 June 04</td>
</tr>
<tr>
<td>1.2</td>
<td>8 July 04</td>
<td>FDA for IND</td>
<td>9 July 04</td>
</tr>
<tr>
<td>2.0</td>
<td>1 October 04</td>
<td>posted on MUST website and link given to potential clinical centers via RFP cover memo</td>
<td>5 October 04</td>
</tr>
<tr>
<td>2.1</td>
<td>16 November 04</td>
<td>CHR</td>
<td>8 December 04</td>
</tr>
<tr>
<td>2.2</td>
<td>5 April 05</td>
<td>CHR</td>
<td>5 April 05</td>
</tr>
<tr>
<td></td>
<td>Clinical Centers with PPM 2</td>
<td>11 April 05</td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>16 May 05</td>
<td>Clinical Centers with PPM 3</td>
<td>20 May 05</td>
</tr>
<tr>
<td>2.3</td>
<td>31 May 05</td>
<td>Clinical Centers with PPM 5</td>
<td>31 May 05</td>
</tr>
<tr>
<td>2.4</td>
<td>28 June 05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Document revision history

Version
1. Protocol 1.0, 5 August 03

2. Protocol 1.1, 2 June 04
   Revisions in response to CHR memo of 25 May 04
   • Clarification that the 0.5 mg fluocinolone acetonide implant will be used and that the dose
     will be the same for all patients. This clarification was added at the bottom of page 4 in
     section 1.5, Rationale and at the top of page 10 in section 4., Treatment Plan.
     • The possibility that record reviewers might see identifying information was added on page
       37, in section 9.2. Confidentiality of patient data, the following sentence was added:
       Also included in the privacy acknowledgment is the statement that representatives of NEI,
       FDA, the Institutional Review Boards, the Coordinating Center, and Bausch and Lomb,
       Inc. may see identifying information while reviewing study records

3. Protocol 1.2
   • Table of Contents, Outcomes, section 6.4: Quality of life removed deleted from TOC in
     error. Section 6.4 returned to TOC on 26 Aug 04.
   • Section 3.1 Design Overview: Change in number of projected clinical centers from 19 to
     20-40 and removed “in the United States”
   • Section 3.2 Enrollment and randomization
     - “Adult” removed as descriptor of patients eligible for MUST.
     - Current use of oral corticosteroids for uveitis (see below), changed to (new text in italics):
       Current or past use of oral corticosteroids or immunosuppressive agents for uveitis is
       acceptable (see below). Previous use of fluocinolone acetonide therapy also is acceptable
       if any implant still present in an eye was placed more than 3 years previously.
     • “Standard therapy” changed to “standardized systemic therapy” throughout
   • Section 3.2.1 Inclusion criteria, clarification added to #3 and “severe” uveitis defined as
     italicized below:
     active uveitis with vitreous cells, inflammatory debris, and/or active choriretinal lesions of
     a degree for which systemic corticosteroid therapy is indicated in the judgment of a MUST-
     certified ophthalmologist ("severe uveitis")
     • “Severe uveitis” used throughout protocol
• **Section 3.2.1 Inclusion Criteria**
  1) changed from 18 to 13 years
  3) added clarification (here in italics): active uveitis with vitreous cells, inflammatory debris, and/or active choriotiretinal lesions of a degree for which systemic corticosteroid therapy is indicated in the judgment of a MUST-certified ophthalmologist (“severe” uveitis); or such uveitis active within the last 30 days as determined either by examination by a MUST-certified ophthalmologist or by review of ophthalmic medical records by a MUST-certified ophthalmologist
  4) added italics text: uveitis with or without an associated systemic disease is acceptable; however, the systemic disease must not be sufficiently active that it dictates therapy with oral corticosteroids or immunosuppressive agents at the time of study entry;

• **Section 3.2.2 Exclusion criteria**
  2) Italicized clarification added:
  A known allergy to a required study medication
  3) Changed from:
  Uncontrolled glaucoma or glaucoma requiring more than two anti-glaucoma medications
  to:
  Uncontrolled glaucoma or glaucoma requiring more than one anti-glaucoma medication in one or more eyes with “severe uveitis”; glaucoma that is controlled following glaucoma surgery is acceptable;
  4) Added new exclusion criterion:
  Advanced glaucomatous optic nerve injury meeting the following criteria:
  • For patients able to perform a Humphrey Visual Field
    1. Depression of two or more points within 10 degrees of fixation by at least 10 dB
    and/or
    2. Mean deviation worse than -15 dB
  • For patients unable to perform a Humphrey Visual Field
    1. Vertical C/D ≥ 0.9

• **4. Treatment plan:**
  — Added as last sentence in first paragraph on page 9:
    Prior to randomization, the enrolling ophthalmologist should list what surgical procedures are currently indicated for each eye on the enrollment form.
  — In second paragraph added italicized text:
    Because post-implantation hypotony appears to occur more commonly in eyes with active anterior chamber inflammation, patients initially should be treated with topical and/or periocular corticosteroids prior to implantation in order to quiet the anterior chamber, which may take up to two weeks. *Oral corticosteroid therapy may be used*
for this purpose when indicated, but should not be used routinely for this purpose

— Added qualification for the timing of the initial implant surgery: implant surgery in the
first eye, while usually required within two weeks of randomization, may be done
within one month of randomization if if a delay is indicated according to best medical
judgment

— Modified criteria as to when the implant should be replaced:
  Deleted italicized text: The implant should be replaced when the first relapse (anterior
  chamber cells and/or vitreous haze grade 1+ or higher (see Section 5.2) of the uveitis
  sufficient to otherwise require systemic corticosteroid therapy occurs in implant-
  treated eyes. Should two relapses in the same eye occur within the first 2.5 years, the
  patient should be treated according to best medical judgment
  Added italicized text: The implant should be replaced if indicated according to best
  medical judgment. Use of implant therapy rather than systemic therapy to control
  relapses of uveitis occurring after an implant is likely to be empty of active drug is
  encouraged, for patients assigned to implant therapy.

— Instructions to insert implant modified:
  “3 clock hour” was removed as a descriptor of conjunctival peritomy. Sentence
  previously read: To insert the implant, a 3 clock hour conjunctival peritomy will be
  made in a site free of these findings, preferably (but not necessarily), in the
  inferotemporal or inferonasal quadrant.

— Instructions for insertion of the implant into the vitreous cavity:
  Clarification added that the implant will be inserted into the vitreous cavity with the
  “cup” facing forward

— Paragraph added to end of Section 4.1 Treatment:
  Patients randomized to implant therapy may have intraocular surgery that was
  indicated at the time of enrollment (and so noted on the enrollment form) performed in
  combination with implant surgery if such combination is in the patient’s best interest
  according to best medical judgment. However, combined vitrectomy surgery to clear
  vitreous opacities should be avoided (inflammatory vitreous opacities are likely to
  clear with implant therapy alone).

• Section 4.2.1 Oral corticosteroid therapy
  — Initial dose of oral corticosteroid therapy
    Previously:
    The initial dose will be 1 mg/kg/day of prednisone, up to a maximum adult oral dose
    of 60 mg/day (“high-dose” prednisone given as one dose in the morning).
    Modified to:
    The initial dose for patients with uveitis that is active at enrollment will be 1
    mg/kg/day of prednisone, up to a maximum adult oral dose of 60 mg/day (“high-dose”
    oral corticosteroid therapy).
—Added option of initial use of intravenous corticosteroids for uveitis control:

*If indicated, according to best medical judgment, intravenous corticosteroids may be used initially, at a dose of up to one gram of methylprednisolone succinate (or equivalent dose of alternative intravenous corticosteroids may be used) each day for three days, followed by “high dose” prednisone (or alternative oral corticosteroid medication) as described above.*

—Modification

Previously:

Patients who at baseline are receiving oral corticosteroid therapy at a dose greater than 10 mg of prednisone and have active uveitis at that dose, also will be started initially on both high-dose prednisone and an additional immunosuppressive drug

Modified to:

Patients who at baseline are receiving oral corticosteroid therapy at a dose greater than 10 mg of prednisone (or equivalent alternative corticosteroid dose) or a lower dose judged to be causing unacceptable corticosteroid-related side effects and have active uveitis at that dose, also will be started initially on both high-dose prednisone and an immunosuppressive drug.

— Instructions added for patients whose uveitis is controlled on oral corticosteroid therapy at randomization:

*Patients whose uveitis already is controlled on oral corticosteroid therapy by the time of randomization will use their current regimen as a starting dosage. If such patients are receiving immunosuppressive therapy at the time of randomization, the immunosuppressive therapy will be continued and handled thereafter as described below.*

— Italicized clarifications made:

If the dose one step above that dose at which the uveitis reactivated is 10 mg/day or less and is sufficiently low to avoid corticosteroid-related adverse effects, it will be considered the “chronic maintenance dose”, and the patient will be continued at that dose for 6 months, after which time tapering by 1 mg/day decrements monthly will be attempted. If the chronic maintenance dose of prednisone will be greater than 10 mg/day or is sufficiently high to cause corticosteroid-induced adverse effects, then an additional immunosuppressive drug (see below) will be added at the time that higher dose prednisone is instituted in response to the uveitis reactivation. After this, the duration of higher dose prednisone therapy, and the tapering schedule will be the same as described previously. If, once again, the suppressive prednisone dose proves to be above 10 mg/day or is a dose sufficiently high to cause corticosteroid-induced adverse effects despite increasing the immunosuppressive agent dosage (if possible), a second immunosuppressive agent will be added (unless contraindicated) as described below,
and high-dose prednisone reinstituted, followed by tapering again in the same manner. If this fails to achieve sustained suppression of uveitis, treatment should be directed by best medical judgment. Likewise, if the suppressive dose of prednisone proves to be above 10 mg/day or sufficiently high to cause corticosteroid-induced adverse effects when an alkylating agent was used as the initial immunosuppressive agent, treatment thereafter should be directed by best medical judgment. All reference to 10 mg/day above refers to prednisone; for alternative oral corticosteroids, a dose equipotent to 10 mg/day of prednisone would be the threshold.

• **Section 4.2.2 Potent immunosuppressive (corticosteroid-sparing) 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.*

• **Section 4.2.2.6 Cyclophosphamide**
  Added dose specification: trimethoprim 80 mg/sulfamethoxazole 400 mg, to be given as prophylactic agent for *Pneumocystis carinii* pneumonia

• **Section 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 aledronate.*

• **Section 5. Data collection**
  — Clarified that, other than the visit one month after randomization, study visits must not be conducted within one month of *intraocular* surgery including implant replacement surgery, cataract surgery, and glaucoma surgery. Previously only implant surgery was mentioned.

  — Table 1: MUST Data Collection Schedule
  ○ Color slit lamp lens photos added at 6 month visit
  ○ Color fundus photos (disc, macula) added at 1 and 6 month visits
  ○ Height will be collected at baseline
  ○ “Quality of life” replaced by “EuroQol” which will be done at baseline and every visit except followup visit 1
  ○ SF-36 and NEI-VFQ added and will be done at baseline, and every 6 months beginning with the 6 month visit
  ○ Casual serum glucose added for 3 month visit; fasting serum glucose deleted from 3 month visit
• **Section 6.1.2 Visual field**
  — Repeat of baseline Humphrey visual field for patients new to visual field tests
  Previously all patients who had never performed a Humphrey visual field would have a “practice” test and then another “real” test in order to avoid to errors that commonly occur at a patient’s first attempt at performing a visual field test. Protocol changed so that only patients who have an abnormal value at baseline will repeat test to avoid errors that commonly occur at a patient’s first attempt at performing a visual field test.

• **Section 6.2 Intraocular inflammation**
  — Changed example of uveitic conditions form serpiginous choroidopathy to serpiginous or birdshot retinochoriopathy
  — Added
    The relationship of inflammation activity to ocular surgery will be evaluated at the time of statistical analysis. Because study visits will take place at least one month after ocular surgery, post-operative inflammation is unlikely to confound grading to inflammation substantially.

• **Section 6.5 Potential ocular complications of uveitis and of therapy**
  — 6.5.1 - Added the italics text in the following sentence: Intraocular pressure 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.
  — 6.5.1 - Clarified that when Tonopen IOP measurement is used, an average of 3 Tonopen measurements will be used.
  — 6.5.2 - Added that the occurrence of cataract will be graded clinically at each study visit using a standardized grading system.

4. **Protocol 2.0**
  — Added document distribution section
  — Added revision history section
  — Corrected reference numbers in text and corrected reference list
  — **Section 5. Data Collection**
  — Added height collection at every visit instead of just baseline
  — **Section 6. Outcomes**
  — Added weight and height measurements to list of outcomes that will be masked

5. **Protocol 2.1**
  — Added cost-effectiveness outcome, section 6.9
  — In section 6.5.2 Cataract, changed grading protocol for posterior capsule opacification in pseudophakic eyes with an intact posterior capsule from use of an ordinal scale to use of the following classification scheme: clear; obscured, not affecting vision, obscured, affect vision; posterior capsule open).
6. Protocol 2.2
   - **Section 1.1 Uveitis definition and classification**
     Added reference by Standardization of Uveitis Nomenclature (SUN) Working Group

   - **Section 1.2 Epidemiology of uveitis**
     Added prevalence and incidence rates per Gritz and Wong, 2004

   - **Section 3.1 [Design] Overview**
     Added: The study will begin under an investigational new drug exemption granted by the Food and Drug Administration (IND #70,211).

   - **Section 4.1 Fluocinolone acetonide**
     Clarification as italicized in following: The implant should be replaced if indicated according to best medical judgment *should relapse of uveitis occur*. Removed specific grading specifications for uveitis suppression and reactivation

   - **Section 5. Data Collection, Table 1**
     Corrected errors as described below:
     Humphrey perimetry changed to 12 months instead of 15 months
     EuroQOL not collected at 3 months
     Changed casual *serum* glucose and fasting *serum* glucose to casual *plasma* glucose and fasting *plasma* glucose
     Casual plasma 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

   - **Section 6.1.2 Visual field**
     Specified that Humphrey visual field testing will use 30-2 SITA-fast protocol. Previously “standard protocol” was specified

   - **Section 6.2 Intraocular inflammation**
     Added that scales endorsed by the SUN Working Group will be used to grade anterior chamber cells, anterior vitreous cells, and vitreous haze when applicable
     Removed specific grading criteria to judge uveitis “inactive” and replaced with statement that Uveitis will be judged to be “inactive” when meeting criteria for inactivity according to the SUN Working Group
     Replaced specific grading criteria with scales endorsed by SUN Working Group to note intraocular inflammation, including anterior chamber flare, at every visit
• **Section 6.5.1 Elevated intraocular pressure and glaucoma**
  Changed specification of protocol used to measure IOP from “protocol followed by the Collaborative Initial Glaucoma Treatment Study” to “a standardized protocol”

  Added clarification that in the case that the two measurements (taken either using Goldman applanation tonometry and Tonopen IOP measurement) differ by ≥ 2 mm Hg, a third measurement will be taken to adjudicate the discrepancy. Removed comment that an average of 3 Tonopen measurements will be used.

  Changed cutoff for elevated IOP from 21 mm Hg to 24 mm Hg

  Added: Rises in IOP by 10 mm Hg will be considered moderate elevations, and a 15 mm Hg rise will be considered a large elevation. Use of IOP-lowering medications will be noted as well.

  Removed: Diagnosis of glaucoma will be made through the integration of several inputs. Stereo optic nerve photographs will be graded by the RC, and reviewed by the glaucoma outcomes committee when abnormalities are noted. Humphrey visual field testing will screen for glaucomatous visual field defects through use of the Glaucoma Hemifield Test, available with the commercial software. Unreliable and/or abnormal results will be evaluated further by repeat testing.

  Added: Regarding the definition of incident glaucoma, we will assess the data accumulated on each subject to determine if glaucomatous optic nerve damage was present at the time of initial IOP elevation, and whether or not it developed or worsened during follow-up. For optic nerves of normal or large size a CDR of 0.7 or greater will be required, for the diagnosis of glaucoma, for small nerves a CDR of 0.6 will be allowed. Smaller CDR will be acceptable if there is a notch. We will also allow for the diagnosis of glaucoma if the CDR differs by 0.3 or more between the two nerves.

  Visual fields will be graded as normal, possible or probable glaucoma taking into account the GHT, PSD and pattern of visual field loss. Two graders will independently assess the visual fields and will adjudicate when in disagreement.

  A final diagnosis of definite, probable, possible or no glaucoma will be made by the consensus of two independent reviewers. If they cannot agree, a third reviewer will be asked to evaluate the data and decide.

• **Section 6.6.1.3 Hyperlipidemia**
  Removed fasting lipid panel conducted at 3 months. Fasting lipid panels will be obtained at baseline and annually thereafter.
• **Section 7.1 Sample Size, power and detectable differences**
  Added sentence: 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

   • **Section 1.4 Fluocinolone acetonide implant therapy for non-infectious uveitis**
     • Section revised to incorporate data released after FDA approval of implant. References 31 and 32 replaced with product insert and 3 May 05 press release.

   • **Section 1.5 Rationale**
     – Changed implant from 0.5 mg to .59 mg

   • **Section 4 Treatment Plan**
     – 0.5 mg fluocinolone acetonide intraocular implant changed to 0.59mg

   • **Section 5 Data Collection**
     – Correction made to first footnote:
       The F6, F7, F8, and F9 data collection tables repeat every 12 months until the common study closeout

   • **Section 6.1.2 Visual Field**
     – Changed Humphrey visual field protocol from 30-2 to 24-2

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

   • **Section 5 Data Collection**
     – Corrected typographical errors in data collection table (gonioscopy, color slit lamp photos, color fundus photos, FA, Oct)

9. **Protocol 2.4 (30 June 05)**

   • **Section 4.1 Fluocinolone acetonide implant therapy**
     – Changed length of interval between first and second eye surgeries from: If both eyes are to receive implants, second eye surgery will be performed **within one week of the first eye’s surgery.** to: If both eyes are to receive implants, second eye surgery will be performed **within two weeks of the first eye’s surgery** (within one month if a delay is indicated, according to best medical judgment).
• **Section 4.2.2 Potent immunosuppressive (corticosteroid-sparing) drugs**
  – Changed liver function to liver enzymes

• **Section 4.2.2.5 Tacrolimus**
  – Changed dosing and monitoring guidelines to the following: Tacrolimus will be initiated at a dose of 1 mg twice daily in adults, or 0.03-0.05 mg/kg/day divided over two doses for persons less than adult size. Doseage may be increased, as indicated, up to a maximum dose of 0.08 mg/kg/day divided over two doses. Monitoring of blood levels, with a target trough range of 8-12 ng/L, is recommended. Patients receiving tacrolimus will have monthly monitoring of blood pressure, hematology, and chemistry, including serum creatinine and liver enzymes. Dose adjustment and interruption of therapy will be performed using the guidelines outlined for the antimetabolites and for cyclosporine.

• **Section 4.2.3 Biologics**
  – Added entire section including 4.2.3.1 - 4.2.3.2

• **Section 5 Data collection**
  – Revised table to include height measurement at annual visit only (previously height to be measured at every visit)
### Contents

Document distribution .......................................................... i

Document revision history ...................................................... ii

Source Documents ............................................................ xv

Abstract ................................................................. xvi

1. Introduction ............................................................... 1
   1.1 Uveitis: definition and classification ........................................ 1
   1.2 Epidemiology of uveitis .................................................. 2
   1.3 Standard treatment of uveitis .............................................. 2
   1.4 Fluocinolone acetonide implant therapy for non-infectious uveitis ................. 3
   1.5 Rationale .............................................................. 5

2. Objectives and Study Hypotheses .............................................. 6
   2.1 Specific aims of the MUST Trial ........................................... 6
   2.2 Study hypotheses ....................................................... 6

3. Design ................................................................. 7
   3.1 Overview ............................................................. 7
   3.2 Enrollment and randomization ............................................. 7
      3.2.1 Inclusion criteria .............................................. 7
      3.2.2 Exclusion criteria ............................................. 8
   3.3 Randomization ......................................................... 9

4. Treatment plan ........................................................... 10
   4.1 Fluocinolone acetonide implant therapy .................................... 10
   4.2 Systemic therapy ...................................................... 11
      4.2.1 Oral corticosteroid therapy ........................................ 11
      4.2.2 Potent immunosuppressive (corticosteroid-sparing) drugs ............ 13
         4.2.2.1 Azathioprine ......................................... 14
         4.2.2.2 Methotrexate ......................................... 14
         4.2.2.3 Mycophenolate mofetil .................................. 14
         4.2.2.4 Cyclosporine ......................................... 14
         4.2.2.5 Tacrolimus ........................................... 15
         4.2.2.6 Cyclophosphamide ..................................... 15
         4.2.2.7 Chlorambucil ......................................... 15
      4.2.2.8 Additional considerations for alkylating agent therapy ......... 16
4.2.3 Biologics ................................................... 16
  4.2.3.1 Infliximab ............................................ 16
  4.2.3.2 Daclizumab .......................................... 17
  4.2.3.3 Other Biologics ....................................... 17

4.3 Ancillary therapy ...................................................... 17
  4.3.1 Topical corticosteroid therapy .................................. 17
  4.3.2 Periocular corticosteroid therapy ............................... 17
  4.3.3 Intraocular corticosteroid injection ............................... 18
  4.3.4 Non-steroidal anti-inflammatory therapy .......................... 18
  4.3.5 Acetazolamide therapy ........................................ 18
  4.3.6 Ancillary therapy for prevention or treatment of adverse effects of systemic therapy .................................................... 18

5. Data Collection ........................................................... 19

6. Outcomes ............................................................... 21
  6.1 Visual function ........................................................ 21
    6.1.1 Visual acuity ................................................ 21
    6.1.2 Visual field ................................................. 22
  6.2 Intraocular inflammation ................................................ 22
  6.3 Retinal morphology .................................................... 23
  6.4 Quality of life ......................................................... 24
  6.5 Potential ocular complications of uveitis and of therapy ............... 24
    6.5.1 Elevated intraocular pressure and glaucoma ....................... 24
    6.5.2 Cataract .................................................... 25
    6.5.3 Other ocular complications ..................................... 25
  6.6 Potential systemic complications of therapy ................................. 25
    6.6.1 Potential complications of corticosteroid therapy .................... 25
      6.6.1.1 Hyperglycemia and diabetes mellitus ............................ 25
      6.6.1.2 Osteoporosis ........................................ 26
      6.6.1.3 Hyperlipidemia ....................................... 26
      6.6.1.4 Hypertension ......................................... 27
      6.6.1.5 Weight and height ..................................... 27
      6.6.1.6 Other potential systemic complications of corticosteroid therapy .................................................... 27
    6.6.2 Potential systemic complications of other immunosuppressive therapy ... 27
      6.6.2.1 Bone marrow suppression .................................... 28
      6.6.2.2 Hepatotoxicity ........................................ 28
      6.6.2.3 Nephrotoxicity .......................................... 28
      6.6.2.4 Other systemic complications .................................. 28
  6.7 Mortality ............................................................. 29
  6.8 Adverse events reporting ................................................ 29
  6.9 Cost-effectiveness ..................................................... 29
### MUST Trial Protocol

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.9.1 Analytic Result</td>
<td>29</td>
</tr>
<tr>
<td>6.9.2 Effectiveness Measures</td>
<td>30</td>
</tr>
<tr>
<td>6.9.2.1 QALYs</td>
<td>30</td>
</tr>
<tr>
<td>6.9.2.2 Other Outcomes</td>
<td>31</td>
</tr>
<tr>
<td>6.9.3 Cost</td>
<td>31</td>
</tr>
<tr>
<td>6.9.4 Perspective</td>
<td>32</td>
</tr>
<tr>
<td>6.9.5 Discount Rate</td>
<td>32</td>
</tr>
<tr>
<td>6.9.6 Inflation</td>
<td>32</td>
</tr>
<tr>
<td>7. Biostatistics</td>
<td>33</td>
</tr>
<tr>
<td>7.1 Sample size, power and detectable differences</td>
<td>33</td>
</tr>
<tr>
<td>7.2 Statistical analysis</td>
<td>33</td>
</tr>
<tr>
<td>8. Data and Safety Monitoring</td>
<td>36</td>
</tr>
<tr>
<td>9. Patient rights and responsibilities</td>
<td>37</td>
</tr>
<tr>
<td>9.1 IRB approvals</td>
<td>37</td>
</tr>
<tr>
<td>9.2 Confidentiality of patient data</td>
<td>37</td>
</tr>
<tr>
<td>10. Biohazards</td>
<td>38</td>
</tr>
<tr>
<td>Reference list</td>
<td>39</td>
</tr>
<tr>
<td>Protocol Committee</td>
<td>45</td>
</tr>
</tbody>
</table>
Source Documents

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
Abstract

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 is a surgically implanted reservoir of corticosteroid designed to last approximately 2.5 years in order to provide long-term control of uveitis.

The primary objective of the Multicenter Uveitis Steroid Treatment (MUST) Trial is 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. Patients with active uveitis will be randomized, with a 1:1 allocation ratio, to treatment with either the fluocinolone acetonide implant or standardized systemic therapy consisting of oral corticosteroids and supplementary immunosuppressive drugs when indicated, according to standardized guidelines. The design outcome variable for the study is visual acuity; other outcomes include other aspects of visual function, success in controlling uveitis, retinal morphologic outcomes, quality of life, cost-effectiveness, and occurrence of potential ocular and systemic complications of uveitis and of therapy.
1. Introduction

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, 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. 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, as updated by the Standardization of Uveitis Nomenclature Working Group, 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. Clinical experience suggests that most cases of posterior uveitis and panuveitis require chronic, suppressive systemic corticosteroid therapy to control inflammation adequately.
1. Introduction

1.2 Epidemiology of uveitis

In western countries, the best available published estimates of the prevalence and incidence rates for uveitis are 38/100,000 and 17/100,000/year respectively,18 based on studies from Germany,19 France,20 and Rochester, Minnesota.21 This prevalence estimate, applied to the United States population in the year 2000, suggests that about 114,000 persons currently have uveitis, most 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 about 1% of persons will be affected by uveitis during their lifetime. A recent report from a Northern California health maintenance organization cohort found higher prevalence (115.3/100,00) and incidence (52.4/100,000 person-years) rates for uveitis, suggesting uveitis may be a larger problem than previously thought.22

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.23 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 1970.24 A recent 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.25

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.26 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;27 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) visual loss.

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,28 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.17

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.29 In addition, for certain specific uveitis syndromes (e.g., Behçet’s disease involving the posterior segment,29 serpiginous choroidopathy30), 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.29 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.29

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 months, and can be replaced if needed.31

In a phase 2/3 clinical trial comparing 0.59 to 2.1 mg versions of the implant,32 278 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.

Additional safety data are available from phase 1/2 studies. As of May 2002, a total of 35 eyes had been treated with either the 2.0 mg or 0.5 mg implant. Among 26 eyes treated with the 2 mg implant, 9 (35%) developed intraocular pressure (IOP) elevation, defined as an IOP elevation of 7 mm Hg or more above baseline sustained for two consecutive visits, 3 requiring removal of the implant, the others controlled medically. Among the 9 eyes treated with the 0.5 mg implant, 1 (11%) developed intraocular pressure elevation, which was controlled medically. Among eyes of uveitis patients, 3/16 (19%) receiving 2 mg implants and 0/3 receiving the 0.5 mg implant developed intraocular pressure elevation. Two eyes of the same patient required surgery for IOP control, and the eye of the other was managed with medical therapy. Cataract requiring cataract surgery did not occur in eyes with uveitis, but an unspecified number were pseudophakic preoperatively. For eyes with the other diseases, 6/10 (60%) treated with the 2 mg implant and 0/6 treated with the 0.5 mg implant required cataract surgery. Other complications, among the 52 eyes that received implants of any dose, included 2 retinal detachments, one optic neuropathy that resolved after implant removal, and small numbers of cases that reported floaters, hypotony, dislocated implant, discomfort, and conjunctival thinning (< 5% each). There were also 5 cases of a retinal vein occlusion syndrome (3 with 6 implants, 2 with 2 implants), which manifested as visual disturbances, disc edema, and intraretinal hemorrhages, all of which occurred after cataract surgery in post-vitrectomy eyes with AMD; all resolved after implant removal. There also were several cases of mild vitreous hemorrhage.

In addition, the product label 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 dihiscence." 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 these uncontrolled observations, the fluocinolone acetonide implant appears to be a promising treatment for severe cases of uveitis, which may have advantages and disadvantages in comparison with standard systemic therapy. The MUST Trial will 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.
2. Objectives and Study Hypotheses

2.1 Specific aims of the MUST Trial:

1) To compare the visual outcomes of patients with uveitis treated with the sustained-release intraocular fluocinolone acetonide implant therapy to those treated with systemic therapy using oral corticosteroids supplemented by corticosteroid-sparing immunosuppressive drugs when indicated;

2) To compare the efficacy of the alternative treatment strategies for controlling uveitis and ameliorating/preventing structural complications of uveitis over time;

3) To compare the rates of local ocular corticosteroid-induced complications and the rates of systemic complications between the treatment groups;

4) To compare the self-reported quality of life of the treatment groups.

2.2 Study hypotheses:

1) Patients randomized to implant therapy will have better visual outcomes.

2) Patients randomized to implant therapy will have improved control of uveitis, a decreased rate of posterior segment structural complications of the uveitis (such as cystoid macular edema and epiretinal membranes), and an increased rate of corticosteroid-induced ocular complications, such as cataracts, ocular hypertension, and glaucoma.

3) Patients randomized to systemic therapy will have a higher rate of systemic complications, such as diabetes, hypertension, and osteoporosis.

4) Improved visual outcomes and the absence of systemic corticosteroid complications (and the additional treatments needed to combat them) will result in a better quality of life for patients randomized to implant therapy.
3. Design

3.1 Overview

The Multicenter Uveitis Steroid Treatment (MUST) Trial is a randomized controlled clinical trial comparing two treatments for patients with vision-threatening non-infectious intermediate uveitis, posterior uveitis, or panuveitis: 1) local therapy with fluocinolone acetonide intraocular implant in all affected eyes; versus 2) systemic corticosteroid therapy supplemented, when indicated, by corticosteroid-sparing potent immunosuppressive therapy. Patients will be enrolled at approximately 21 clinical centers and randomized on a 1:1 basis to one of the two treatment groups. Participants will be followed until death, participant withdrawal, or a common study closeout. Patients will be seen at baseline, one month after randomization, three months after randomization, and every three months thereafter 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. A sample size of 400 patients, 200 per treatment group, is expected to give sufficient power to detect clinically important differences in visual acuity outcomes. The trial will be monitored by a Data and Safety Monitoring Committee, with authority to recommend modification or termination of the trial based on review of interim analyses of efficacy and safety data. The study will begin under an investigational new drug exemption granted by the Food and Drug Administration (IND #70,211).

3.2 Enrollment and randomization

Patients with active non-infectious intermediate uveitis, posterior uveitis, or panuveitis for whom oral corticosteroid therapy is indicated are eligible for the MUST Trial. Current or past use of oral corticosteroids or immunosuppressive agents for uveitis is acceptable (see below). Previous use of fluocinolone acetonide therapy also is acceptable if any implant still present in an eye was placed more than 3 years previously.

3.2.1 Inclusion criteria:

1) Age 13 years or older;

2) Diagnosis of non-infectious intermediate uveitis, posterior uveitis, or panuveitis by a MUST-certified ophthalmologist;

3) Active uveitis with vitreous cells, inflammatory debris, and/or active chorioretinal lesions of a degree for which systemic corticosteroid therapy is indicated in the judgment of a MUST-certified ophthalmologist (“severe” uveitis); or such uveitis active within the last 30 days as determined either by examination by a MUST-certified ophthalmologist or by review of ophthalmic medical records by a MUST-certified ophthalmologist.
3. Design

4) Uveitis with or without an associated systemic disease is acceptable; however, the systemic disease must not be sufficiently active that it dictates therapy with oral corticosteroids or immunosuppressive agents at the time of study entry;

5) Best-corrected visual acuity (BCVA) better than 20/200 (35 letters) on a ETDRS logarithmic visual acuity chart in at least one eye with “severe uveitis”

6) Baseline intraocular pressure 24 mm Hg or less in all eyes with “severe uveitis”

7) Media clarity sufficient to allow visualization and imaging of the fundus in at least one eye with “severe uveitis”;

8) Collection of required baseline data within 10 days prior to randomization;

9) Signed informed consent.

3.2.2 Exclusion criteria:

1) Diabetes mellitus that is inadequately controlled, according to best medical judgment;

2) A known allergy to a required study medication;

3) Uncontrolled glaucoma or glaucoma requiring more than one anti-glaucoma medication in one or more eyes with “severe uveitis”; glaucoma that is controlled following glaucoma surgery is acceptable.

4) Advanced glaucomatous optic nerve injury meeting the following criteria:
   • For patients able to perform a Humphrey Visual Field
     1. Depression of two or more points within 10 degrees of fixation by at least 10 dB
     and/or
     2. Mean deviation worse than -15 dB
   • For patients unable to perform a Humphrey Visual Field
     1. Vertical C/D ≥ 0.9

5) A history of scleritis (because of concerns regarding the potential for scleral melting with local corticosteroid therapy);

6) Presence of an ocular toxoplasmosis scar;

7) Pregnancy;

8) Current breastfeeding;
3. Design

9) Known human immunodeficiency virus infection or other immunodeficiency disease for which corticosteroid therapy would be contraindicated according to best medical judgment;

10) Patients for whom participation in the trial would constitute a risk exceeding the potential benefits of study participation, in the judgment of the treating physician;

11) Medical problems or drug or alcohol dependence problems sufficient to prevent adherence to treatment and study procedures.

3.3 Randomization

After the patient has given written informed consent, and baseline data have been keyed and passed an electronic eligibility review, the patient will be randomly assigned to one of the two treatment groups, via a web-based system, returning the treatment assignment result in real time. Receipt of treatment assignment will be confirmed by user re-entry of the treatment assignment. Beginning at this point, the subject’s data will be included for primary analyses, regardless of subsequent actual treatment and/or extent of adherence to therapy.

Randomization will be accomplished using an auditable, documented scheme generating a reproducible order of assignment. Randomization schedules will be developed by the Coordinating Center (CC), using permuted blocks of varying lengths, designed to yield expected assignment ratio of 1:1. Randomization will be stratified by clinical center, and by type of uveitis: 1) intermediate uveitis; and 2) posterior uveitis or panuveitis (the rate of vision loss is similar in posterior uveitis and panuveitis, but lower in intermediate uveitis26).
4. Treatment plan

Patients will be randomized 1:1, by patient, to treatment with either the 0.59 mg fluocinolone acetonide intraocular implant or oral corticosteroids, supplemented by potent immunosuppressive therapy when indicated according to standard criteria. Prior to randomization, the enrolling ophthalmologist should list what surgical procedures are currently indicated for each eye on a study form.

4.1 Fluocinolone acetonide implant therapy

Patients randomized to fluocinolone implant therapy will receive a fluocinolone acetonide implant in each eye with “severe uveitis” (defined as uveitis for which systemic corticosteroid therapy is indicated): patients with unilateral “severe uveitis” will receive unilateral implants, and those with bilateral “severe uveitis” will receive bilateral implants. Second eyes of patients with unilateral disease assigned to the implant group who develop uveitis activity to a degree for which systemic therapy is indicated after treatment assignment will receive implant therapy at the time it becomes indicated.

Because post-implantation hypotony appears to occur more commonly in eyes with active anterior chamber inflammation, patients initially should be treated with topical and/or periocular corticosteroids prior to implantation when needed in order to quiet the anterior chamber, which may take up to two weeks. Oral corticosteroid therapy may be used for this purpose when indicated, but should not be used routinely for this purpose. Fluocinolone acetonide implant surgery then will proceed in the first eye within two weeks of the first eye's surgery (within one month if a delay is indicated, according to best medical judgment). If both eyes are to receive implants, second eye surgery will be performed within two weeks of the first eye's surgery (within one month if a delay is indicated according to best medical judgment). If there is an adverse outcome of the first implant surgery which makes implantation of the second eye contraindicated, then treatment of the second eye should proceed according to best medical judgment.

Surgical implantation will be performed by a MUST-certified implant surgeon under routine anesthesia. The fluocinolone acetonide intraocular implant is designed to last for 2.5-3 years. The implant should be replaced if indicated according to best medical judgment should relapse of uveitis occur. For patients assigned to implant therapy, use of implant therapy rather than systemic therapy to control relapses of uveitis occurring after an implant is likely to be empty of active drug is encouraged.

To prepare the implant, a double-armed 8-0 or 9-0 prolene suture will be threaded through the hole in the base of the strut. The corners of the distal end of the strut may be rounded further if desired. Prior to placement of the implant, the peripheral retina should be carefully examined to identify an area without snowbanking or peripheral traction retinal detachment. To insert the implant, a conjunctival peritomy will be made in a site free of these findings, preferably (but not
necessarily), in the inferotemporal or inferonasal quadrant. Cautery will be used to achieve hemostasis. A microvitreal or supersharps blade will be used to make a full thickness eye wall incision 4 mm posterior to the limbus, which will be enlarged circumferentially to 3.5 mm in length. Prolapsed vitreous will be excised using an automated vitrectomy device. The lips of the incision will be spread with forceps to verify that a full-thickness incision has been made, after which the implant will be inserted into the vitreous cavity with the “cup” facing forward. After verification of intravitreal placement by transpupillary examination, the arms of the double-armed 8-0 or 9-0 prolene suture will be used to pass a deep scleral anchoring suture through the anterior and posterior lips of the midpoint of the sclerotomy incision. The knot of this anchoring suture will be secured and the ends left long and parallel to the incision. The incision then will be closed with additional sutures. Long ends of the anchoring suture should be secured beneath the closing sutures. Saline solution should be injected into the vitreous cavity to restore normal intraocular pressure, if needed. The conjunctiva will be closed with two plain 6-0 collagen or similar sutures. In eyes which have previously undergone vitrectomy, it may be necessary to place an infusion cannula in order to maintain intraocular pressure during the implantation procedure.

Patients taking oral corticosteroid therapy at baseline who are assigned to implant therapy will be tapered off of oral corticosteroids after implant placement. The taper schedule should take into account the potential for adrenal suppression if chronic oral corticosteroid therapy has been used.

If patients randomized to implant therapy require systemic corticosteroid or other immunosuppressive therapy during the MUST Trial, the specific indications for such therapy (either for management of systemic disease or for management of uveitis under the "best medical judgment" portion of the treatment protocol) will be noted on the followup medical history form.

Patients randomized to implant therapy may have intraocular surgery that was indicated at the time of enrollment (and so noted on the study form) performed in combination with implant surgery if such combination is in the patient’s best interest according to best medical judgment. However, combined vitrectomy surgery to clear vitreous opacities should be avoided (inflammatory vitreous opacities are likely to clear with implant therapy alone).

4.2 Systemic therapy

4.2.1 Oral corticosteroid therapy

Patients randomized to systemic therapy will receive oral corticosteroid therapy in accordance with the “Guidelines for the Use of Immunosuppressive Drugs in Patients with Ocular Inflammatory Disorders: Recommendations of an Expert Panel.” The initial dose for patients with uveitis that is active at enrollment will be 1 mg/kg/day of prednisone, up to a maximum adult oral dose of 60 mg/day (“high-dose” oral corticosteroid therapy). Patients will be treated with oral prednisone at the initial dose until the uveitis is controlled, or until the patient has been on this dose of prednisone for one month. An equipotent dose of an alternative oral corticosteroid medication can be used if a
specific contraindication to prednisone exists. If indicated, according to best medical judgment, intravenous corticosteroids may be used initially, at a dose of up to one gram of methylprednisolone succinate (or equivalent dose of an alternative intravenous corticosteroid may be used) each day for three days, followed by “high dose” prednisone (or alternative oral corticosteroid medication) as described above. If there is worsening or no improvement in inflammation after 2-4 weeks, or if the uveitis is not completely controlled after four weeks of high-dose oral prednisone, an immunosuppressive drug will be added, as outlined below. Patients with selected disorders, where oral corticosteroids alone are inadequate as initial therapy (e.g., Behçet’s disease with retinal vasculitis, serpiginous choroiditis²⁹,³⁰) will be started on both prednisone and an immunosuppressive drug. Patients who at baseline are receiving oral corticosteroid therapy at a dose greater than 10 mg of prednisone (or equivalent alternative corticosteroid dose) or a lower dose judged to be causing unacceptable corticosteroid-related side effects and have active uveitis at that dose, also will be started initially on both high-dose prednisone and an immunosuppressive drug.

Patients whose uveitis already is controlled on oral corticosteroid therapy by the time of randomization will use their current regimen as a starting dosage. If such patients are receiving immunosuppressive therapy at the time of randomization, the immunosuppressive therapy will be continued and handled thereafter as described below.

If suppression of uveitis is achieved the oral corticosteroid dosage will be tapered. Prednisone will be tapered as follows: 1) 10 mg decrements in the daily dosage each week to 40 mg daily; 2) 5 mg decrements in the daily dosage each week to 20 mg daily; 3) 2.5 mg decrements in the daily dosage each week to 10 mg daily; and 4) below 10 mg/day, the dose will be decreased by 1 to 2.5 mg decrements in the daily dosage every two to four weeks until the patient is off of prednisone. Alternative corticosteroids, when indicated, should be tapered so as to maintain a schedule as close to equipotent as possible for each time interval to that outlined for prednisone. If the uveitis reactivates, the prednisone should be increased again to a dose of 1 mg/kg (maximum of 60 mg) of prednisone (or, for mild reactivations, to a dose double that at which the flare occurred) until uveitis is controlled, then tapered, following the same tapering schedule, until arrival at a dose level one step above that dose at which the uveitis reactivated. If the dose one step above that dose at which the uveitis reactivated is 10 mg/day or less and is sufficiently low to avoid corticosteroid-related adverse effects, it will be considered the “chronic maintenance dose”, and the patient will be continued at that dose for 6 months, after which time tapering by 1 mg/day decrements monthly will be attempted. If the chronic maintenance dose of prednisone will be greater than 10 mg/day or is sufficiently high to cause corticosteroid-induced adverse effects, then an additional immunosuppressive drug (see below) will be added at the time that higher dose prednisone is instituted in response to the uveitis reactivation. After this, the duration of higher dose prednisone therapy, and the tapering schedule will be the same as described previously. If, once again, the suppressive prednisone dose proves to be above 10 mg/day or is a dose sufficiently high to cause corticosteroid-induced adverse effects despite increasing the immunosuppressive agent dosage (if possible), a second immunosuppressive agent will be added (unless contraindicated) as described below, and high-dose prednisone reinstated, followed by tapering again in the same manner. If this fails to achieve sustained suppression of uveitis, treatment should be directed by best medical judgment. Likewise, if the suppressive dose of prednisone proves to be above 10 mg/day or sufficiently high to cause
corticosteroid-induced adverse effects when an alkylating agent was used as the initial immunosuppressive agent, treatment thereafter should be directed by best medical judgment. All reference to 10 mg/day above refers to prednisone; for alternative oral corticosteroids, a dose equipotent to 10 mg/day of prednisone would be the threshold used in the decision tree described here.

After 6 months of suppression of uveitis on chronic suppressive oral corticosteroid therapy (with or without immunosuppressive therapy), an attempt will be made to taper the prednisone further with monthly decrements following the steps above. If such tapering results in reactivation of uveitis, the prednisone dose will be raised sufficiently to control the uveitis, and then tapered again to the suppressive dose. The patient will be kept on chronic prednisone therapy at the suppressive dose for at least 12 months before further tapering attempts.

4.2.2 Potent immunosuppressive (corticosteroid-sparing) drugs

Immunosuppressive drugs will be used according to the "Guidelines for the Use of Immunosuppressive Drugs in Patients with Ocular Inflammatory Disorders: Recommendations of an Expert Panel."29 Immunosuppressive drugs permitted in this trial include the antimetabolites azathioprine, methotrexate, and mycophenolate mofetil; the T-cell inhibitors cyclosporine, and tacrolimus; and the alkylating agents, cyclophosphamide, and chlorambucil. Other drugs may be used for patients who are being treated under the "best medical judgment" provisions of the protocol. Although the immunosuppressive drug to be used will be determined based upon clinical judgment considering the patient’s other medical conditions, each drug will be used in a protocol-directed fashion. Because of the potential additive therapeutic effect of antimetabolites and T-cell inhibitors, patients not achieving an adequate response to therapy with one immunosuppressive drug will have a second immunosuppressive drug of the alternative class added, if not contraindicated. However, an attempt to maximize the effect of a single agent by upward dose-adjustment should be attempted, when not contraindicated, before adding a second agent. Because of the potential for side effects (usually reversible), monitoring will occur as outlined below, with dose adjustment as necessary when signs of toxicity are observed.

All patients to receive immunosuppressive drugs will be informed in advance of the potential side effects of the specific drug to be used. Standardized patient education sheets discussing potential side effects will be made available to study sites. Because of the potential for teratogenic effects, all women of child bearing age should practice appropriate contraception. Men receiving methotrexate similarly should practice appropriate contraception. For patients who develop toxicity while using one drug, an alternative immunosuppressive drug may be substituted. Alkylating agents (cyclophosphamide and chlorambucil), although given in conjunction with corticosteroids, will not be combined with other immunosuppressive drugs because of the potential for substantially increased toxicity in that setting. 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. Treatment Plan

4.2.2.1 Azathioprine

Azathioprine will be used at a dose of approximately 2 mg/kg/day (100-150 mg/day). An optional test dose of 50 mg/day for one week is permitted. If unable to achieve therapeutic goals with the initial dosage, the azathioprine dose may be increased up to a maximum of 200 mg/day. Patients receiving azathioprine will have a complete blood count and liver enzymes each month to monitor for potential toxicity. The dose of azathioprine should be adjusted for mild decreases in platelet count and mild elevations of liver enzymes results. For evidence of more severe toxicity (e.g., white blood count 2500/μL or lower, liver enzymes 5 times upper limit of normal or higher), azathioprine therapy should be interrupted temporarily, but may be resumed after a return to the normal range, unless contraindicated.

4.2.2.2 Methotrexate

Methotrexate will be given at an initial dose of 15 mg by mouth once weekly. An optional initial test dose of 7.5 mg the first week is permitted. If unable to achieve therapeutic goals with the initial dosage, the dose of methotrexate may be increased up to a maximum of 25 mg weekly. Patients receiving methotrexate also will be given folate 1 mg/day in order to minimize methotrexate side effects. Complete blood count and liver enzymes will be obtained monthly to monitor for possible toxicity. Mild decreases in white blood count or elevations of liver enzymes should prompt dose adjustment. More severe lowering of blood cell counts or elevations of liver enzymes results (see azathioprine) will result in interruption of methotrexate therapy. Methotrexate also may be given subcutaneously if desired, at the same dosage.

4.2.2.3 Mycophenolate mofetil

Mycophenolate mofetil will be administered at a dose of 1 gm orally twice daily. Patients on mycophenolate mofetil will have a complete blood count and chemistry panel, including liver enzymes, monthly. Dose adjustment of mycophenolate mofetil (up to a maximum dosage of 1.5 gm orally twice daily) and interruption of drug therapy will be performed according to guidelines for azathioprine and methotrexate as outlined above.

4.2.2.4 Cyclosporine

Cyclosporine will be given using the microemulsification preparation (Neoral) at a dose of 2.5 mg/kg twice daily. The dose will be adjusted based on clinical response and side effects (maximum dosage of 10 mg/kg daily). Blood pressure, serum creatinine and liver enzymes will be checked monthly to monitor for potential toxicity. Patients with elevations of blood pressure (>140/90) will be referred to their primary care physician for management of hypertension. Patients for whom adequate blood pressure control cannot be achieved with antihypertensive agents will have the cyclosporine dosage decreased; or will discontinue cyclosporine therapy, if a decreased dosage fails. Patients whose creatinine level increases by 30% from baseline while remaining within the normal range, will have the cyclosporine dose reduced. Those who develop an abnormally elevated serum creatinine will have cyclosporine therapy interrupted; after the serum creatinine normalizes,
4. Treatment Plan

cyclosporine may be restarted at 50% of the original dose, with adjustment upward thereafter as needed for clinical response (to a maximum level no higher than 75% of the dose at which abnormally elevated serum creatinine occurred).

4.2.2.5 Tacrolimus

Tacrolimus will be initiated at a dose of 1 mg twice daily in adults, or 0.03-0.05 mg/kg/day divided over two doses for persons less than adult size. Dosage may be increased, as indicated, up to a maximum dose of 0.08 mg/kg/day divided over two doses. Monitoring of blood levels, with a target trough range of 8-12 ng/L, is recommended. Patients receiving tacrolimus will have monthly monitoring of blood pressure, hematology, and chemistry, including serum creatinine and liver enzymes. Dose adjustment and interruption of therapy will be performed using the guidelines outlined for the antimetabolites and for cyclosporine.

4.2.2.6 Cyclophosphamide

Cyclophosphamide will be initiated at a dose of 2 mg/kg/day (approximately 100-150 mg/daily), and escalated as necessary to achieve a clinical effect, up to a maximum of 200 mg/day. Patients also will receive trimethoprim 80 mg/sulfamethoxazole 400 mg prophylaxis for Pneumocystis carinii pneumonia, or, if allergic, an alternative prophylactic agent. Patients receiving cyclophosphamide therapy will be encouraged to drink 2 or more liters of fluid per day in order to maintain “urine flow” in order to minimize bladder toxicity. Patients will have a complete blood count and urinalysis weekly. The dose will be adjusted in order to achieve a white blood cell (WBC) count that would be 3000-4000 cells/μL in the absence of prednisone. Therapy will be temporarily interrupted for a WBC count of 2500 cells/μL or less, followed by reinstitution of the drug at a lower dose. Patients developing hematuria will have cyclophosphamide therapy discontinued, but may be switched to chlorambucil.

4.2.2.7 Chlorambucil

Chlorambucil therapy with either of two approaches will be permitted: 1) patients will be started at a dose of 0.1-0.2 mg/kg/day (6-12 mg daily) as a single daily dose. The dose will be adjusted in order to lower the white count to the same range as described above for cyclophosphamide. Patients will have a complete blood count done each week. Dose adjustment, interruption of therapy, and Pneumocystis carinii pneumonia prophylaxis will be performed using the same guidelines as for cyclophosphamide; 2) for short-term, high-dose chlorambucil therapy, patients will be initiated at a dose of 2 mg daily for one week followed by dose escalation by 2 mg/day each week until the uveitis is suppressed, the WBC count decreases to below 2500 cells/μL, or the platelet count decreases to below 100,000/μL. If other substantial bone marrow toxicity occurs during short-term, high-dose chlorambucil therapy, chlorambucil therapy will be interrupted.
4. Treatment Plan

4.2.2.8 Additional considerations for alkylating agent therapy

Because of the possibility of sterility from alkylating agents (cyclophosphamide and chlorambucil), patients should be informed of this risk and given the opportunity for cryopreservation of eggs or sperm, if desired. Because of the potential for induction of a long-term drug-free remission with alkylating agent therapy, patients receiving alkylating agents will continue to have prednisone tapered and discontinued, rather than stopping at the predicted suppressive dose. If the uveitis reactivates, treatment will be according to best medical judgment. For cases where uveitis is suppressed for one year off prednisone therapy, the alkylating agent therapy will be tapered and discontinued. Approximately 75% of patients given alkylating agent therapy are expected enter a long-term drug-free remission. Because of the potential for substantial toxicity, alkylating agent therapy will not be used in combination with antimetabolite and/or T-cell inhibitor therapy.

4.2.3 Biologics

The class of agents commonly call “biologics”, consisting of monoclonal antibodies against various components of the immune response, have shown considerable promise in the treatment of uveitis. In particular, infliximab and daclizumab now are considered by many uveitis specialists to be part of the armamentarium in the systemic therapy arsenal useful in the treatment of uveitis. Because this area is rapidly evolving, other agents may achieve this status during the course of the MUST trial. Therefore, the trial will permit use of these agents, as described below.

4.2.3.1 Infliximab

Infliximab is a chimeric, humanized monoclonal antibody with high affinity for TNF-α, which is FDA-approved for treatment of Rheumatoid Arthritis, Crohn's Disease, Ankylosing Spondylitis, and Psoriatic Arthritis, at doses of 3 mg/kg (RA) or 5 mg/kg (the other conditions). For most of these conditions, infusions at baseline, two weeks, six weeks, and every eight weeks thereafter are recommended. Increased infusion frequency or higher dosage can be used, up to 10 mg/kg, although doses above 5 mg/kg are contraindicated in congestive heart failure.

Infliximab has been reported to be effective for a range of uveitides, particularly that associated with Behçet's Disease. A variety of dosages have been used; anecdotal data suggest that a dose of 5 mg/kg monthly may be appropriate. However, because consensus is currently lacking, treatment dosages used for uveitis must be individualized. Based on results in other disease settings, concomitant therapy with another immunosuppressive agent may be useful to reduce the development of anti-infliximab antibodies, leading to decreased serum levels and shorter duration of effect. Screening for active or latent tuberculosis, and treatment thereof, is indicated prior to embarking upon infliximab therapy. Periodic monitoring of the complete blood count and serum chemistry results, including liver enzymes, is indicated, based on occasional observations of severe liver injury and hematologic events.
4. Treatment Plan

4.2.3.2 Daclizumab

Daclizumab is a humanized monoclonal antibody binding the IL-2 receptor's α-chain. It is FDA-approved for treatment of renal transplant rejection and has been effectively used for several inflammatory conditions, including as a corticosteroid-sparing agent in uveitis. Based on the available studies in the uveitis setting, a dose of 1 mg/kg/dose up to a maximum of 100 mg/dose given as a slow drip intravenous infusion over 30-60 minutes is recommended, with the following dosage schedule: one infusion every two weeks for the first three months, every three weeks for the next three months, and every four weeks thereafter (until such time as a cessation of therapy is indicated). A subcutaneous approach to daclizumab administration is being studied, but is considered to be preliminary at this time. Preliminary data suggest that use of a concomitant immunosuppressive agent to prevent development of anti-daclizumab antibodies may not be necessary for the majority of patients. A preliminary monitoring schedule for patients treated with daclizumab includes monitoring of a complete blood count and chemistry panel (including liver enzymes, blood urea nitrogen, and serum creatinine) every 4-6 weeks.

4.2.3.3 Other Biologics

Other biologics, such as adalimumab, are likely to come into use for uveitis. Currently data are lacking to guide their use. Therefore, it is recommended that use and monitoring of these agents follow standards that have been developed in their use for treatment of other systemic autoimmune diseases, unless uveitis-specific information becomes available to guide their use.

4.3 Ancillary therapy

4.3.1 Topical corticosteroid therapy

Patients in both treatment arms will be allowed topical corticosteroid therapy when indicated according to best medical judgment. When indicated, topical corticosteroid therapy will be given in a standardized fashion as outlined in the MUST Trial Manual of Procedures. Given the severe nature of the uveitis of patients enrolled in this trial and the limited penetration of topical corticosteroids past the anterior chamber, these drops are unlikely to have a substantial effect on the major causes of visual loss.

4.3.2 Periocular corticosteroid therapy

Periocular injections of corticosteroids will be permitted as ancillary therapy, only when indicated for the following circumstances: 1) for patients randomized to implant therapy, periocular corticosteroids may be given prior to implantation to “quiet the anterior chamber”, which seems to decrease the probability of postoperative hypotony; or 2) for persistent or refractory macular edema in either group. Periocular corticosteroids may be given either via the posterior sub-Tenon's route or via the orbital floor route. The drug and dose used will be triamcinolone acetonide, 40 mg. The route used for periocular corticosteroid therapy, and the number of periocular corticosteroid injections required, will be recorded for comparison between the treatment groups.
4. Treatment Plan

4.3.3 Intraocular corticosteroid injection

Ancillary intraocular corticosteroid therapy, which is not currently an established treatment for uveitis, will not be included in treatment under protocol, except for patients being managed under “best medical judgment”.

4.3.4 Non-steroidal anti-inflammatory therapy

Use of topical and oral non-steroidal anti-inflammatory drugs is permitted at any time during the study, to be used according to best medical judgment. Topical non-steroidal anti-inflammatory therapy is encouraged for patients with recalcitrant macular edema.

4.3.5 Acetazolamide therapy

Use of acetazolamide in an attempt to clear macular edema is permitted at any time during the study and may be applied according to best medical judgment.

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

Patients receiving oral corticosteroids should receive calcium supplementation in order to minimize the incidence of osteoporosis. Unless there is a contraindication (e.g., renal calculi), patients should be given 500 mg of calcium 3 times daily. The calcium preparation should be combined with a small dose of vitamin D (400-800 IU). Suitable combination preparations are available. Unless contraindicated, based on guidelines of the American College of Rheumatology, patients developing osteopenia will receive alendronate at a dose of 35 mg once weekly; those developing osteoporosis will be given alendronate 70 mg once weekly (see section 6.6.1.2 Osteoporosis).

Patients developing hypertension or diabetes from systemically-administered drugs will be referred to their primary care physician for appropriate management. Data regarding the use of antihypertensives and of hypoglycemic agents during the trial will be collected.
5. Data Collection

Patients enrolled in the MUST Trial will have visits for data collection as outlined in Table 1. Other than the visit 1 month after randomization, study visits must not be conducted within one month of intraocular surgery (e.g., implant replacement surgery, cataract surgery, glaucoma surgery), in order to avoid biasing visual acuity measurements downward in postoperative eyes, which are expected to have transiently reduced visual acuity in the early postoperative period. For example, after a patient has had implant replacement surgery in a study eye, a study visit should be scheduled to occur no sooner than 1 month after the implant surgery. Patients generally will receive more frequent visits and may have more frequent laboratory testing performed as indicated for clinical care, but 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, unless such events meet requirements for expedited reports.
### 5. Data Collection

Table 1: MUST Data Collection Schedule

<table>
<thead>
<tr>
<th>Target week</th>
<th>0</th>
<th>4</th>
<th>13</th>
<th>26</th>
<th>39</th>
<th>52</th>
<th>65</th>
<th>78</th>
<th>91</th>
<th>104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit ID</td>
<td>BL</td>
<td>F1</td>
<td>F2</td>
<td>F3</td>
<td>F4</td>
<td>F5</td>
<td>F6*</td>
<td>F7*</td>
<td>F8*</td>
<td>F9*</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Goldmann tonometry</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Ophthalmic Exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Gonioscopy</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color slit lamp lens photos</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Color fundus photos (disk, macula)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optical coherence tomography</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humphrey 24-2 perimeter</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Height</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EuroQol</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SF-36, NEI-VFQ</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensive chemistry panel</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casual plasma glucose</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting lipid analysis</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum pregnancy test</td>
<td>x†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone densitometry</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The F6, F7, F8 and F9 data collection schedules repeat every 12 months until the common study closeout.
† For women who are able to become pregnant

Visual acuity, tonometry, gonioscopy, perimetry, and blood pressure measurements will be obtained prior to pupil dilation. Ophthalmic examination will be conducted both before dilation (grading of anterior chamber cells) and after dilation (funduscope examination, vitreous cells). Photography, angiography, and ocular coherence tomography will be conducted after dilation. Quality of life should be assessed prior to discussion of the day's examination results with the participant, to avoid biasing subjective responses by the day's examination findings. Other measurements may be obtained when most convenient. The choice of which mydriatic agent(s) to be used will not be regulated in the MUST Trial. Measurements of visual acuity and blood pressure will be made by an examiner masked to treatment assignment (see below).

Data obtained will be entered onto paper forms, and then keyed into the electronic database by clinical center personnel over a secure internet connection.
6. Outcomes

Outcomes measured in the MUST Trial 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 the treatments used in the trial. 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. However, because the goal of therapy for uveitis is to preserve vision, the primary outcome will be best-corrected visual acuity. 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.

Masking will be applied to the determination of visual function (at the six month visit and thereafter), those outcomes based on photographic reading, blood pressure measurements, height and weight, laboratory studies, and diagnosis of glaucoma by the glaucoma outcomes committee. Because sham surgery will not be performed, masking during ascertainment of the other outcomes is not feasible.

An adverse events reporting system also will be implemented 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.

6.1 Visual function

6.1.1 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. Ascertainment of visual acuity will be conducted by the unmasked study coordinator at the one month and three month visits. At the baseline, six month, and subsequent visits (by which time surgically treated eyes are expected to look normal), a masked visual acuity examiner will make these measurements. At baseline, visual acuity measurement will be conducted prior to treatment assignment. The design outcome is based on the change in visual acuity (number of letters read) from baseline in eyes meeting trial inclusion criteria (see Section 3) at baseline. Visual acuity data also will be analyzed in several different ways, such as the proportion with low vision (worse than 20/40) and legal blindness (20/200 or worse, and/or visual field subtending an angle of 20 degrees or less) over time, etc. Visual acuity outcomes will be evaluated both from the "by patient" (both for the worse eye and for the better eye, only eyes with "severe uveitis"), and the "by eye" (only eyes with "severe uveitis") perspectives.
6. Outcomes

6.1.2 Visual field

Humphrey visual field testing, using the 24-2 SITA-fast protocol, will be performed at baseline, 12 months, and every 12 months thereafter. 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 retinochoroidopathies, will be used for analyses of efficacy in this subset of patients, after adjusting for the effects of glaucoma and cataract. For patients who have abnormal baseline values, the test will be repeated to verify a true abnormality in order to avoid the errors that commonly occur at a patient's first attempt at performing a visual field test. For patients who initially have a normal visual field result, a single “baseline” visual field will suffice.

6.2 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, trace, 1+, 2+, 3+, 4+)\textsuperscript{13,50,51} using the scales endorsed by the Standardization of Uveitis Nomenclature Working Group\textsuperscript{16} when applicable.

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

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\textsuperscript{16}) 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, and 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

To document the ocular abnormalities of uveitis and its complications, fundus photographs, fluorescein angiograms 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 masked graders according to standardized protocols, at baseline and longitudinally. The resultant data will be summarized into analysis variables, and transmitted to the Coordinating Center. The details of these procedures are available in the Study 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 primarily by fluorescein angiography (FA), supplemented by ocular coherence tomography (OCT) and color fundus photographs. When edema is present, the severity of fluorescein leakage and of cystoid spaces will be assessed, using a modification of the ETDRS protocol. The area in disc areas of retinal thickening and of cystoid spaces found on concurrently graded FA and color fundus photographs also will be evaluated. The extent of fluorescein leakage also will be graded (in disc areas). Central macular thickness will be measured by OCT. Thus, measures of all three dimensions of the extent of macular edema will be obtained. The association of these measures with visual acuity will be assessed; indices of macular edema (increased retinal thickness) are expected to be strongly related to reduced visual acuity.

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

- vascular non-perfusion (FA)
- choroidal neovascularization (FA)
- preretinal neovascularization (color fundus photographs, FA)
- vitreoretinal interface abnormalities (OCT, color fundus photographs)
- retinal detachment (color fundus photographs, FA)
- optic disc edema/fluorescein staining of optic disc (FA, 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 patients 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.
6. Outcomes

6.4 Quality of life

Severe uveitis is expected to affect 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 Trial QOL battery will consist 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. The EuroQol is a generic health index that is widely used in clinical research to calculate a health utility, which is useful as a summary indicator of a patient'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.

6.5 Potential ocular complications of uveitis and of therapy

6.5.1 Elevated intraocular pressure and glaucoma

Intraocular pressure 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. Intraocular pressure (IOP) will be measured using a standardized protocol before gonioscopy or dilation. A certified technician will operate a Goldmann applanation tonometer, while a second observer records the findings. The second observer then will reset the tonometer, and the measurement will be repeated. Tonopen (Mentor Ophthalmics, Norwell, Massachusetts) IOP measurement will be acceptable if Goldmann tonometry cannot be performed. In either case, if the two measures differ by $\geq 2$ mm Hg, a third measurement will be made to adjudicate the discrepancy. Intraocular pressure measurements above 24 mm Hg will be considered elevated, and measurements above 30 mm Hg will be considered highly elevated. Rises in IOP by 10 mm Hg will be considered moderate elevations, and a 15 mm Hg rise will be considered a large elevation. Use of IOP-lowering medications will be noted as well.

Clinicians also will indicate whether they suspect glaucomatous optic nerve injury has occurred on an ordinal scale (absent, glaucoma suspect, probable glaucoma, definite glaucoma). Regarding the definition of incident glaucoma, we will assess the data accumulated on each subject to determine if glaucomatous optic nerve damage was present at the time of initial IOP elevation, and whether or not it developed or worsened during follow-up. For optic nerves of normal or large size a CDR of 0.7 or greater will be required, for the diagnosis of glaucoma, for small nerves a CDR of 0.6 will be allowed. Smaller CDR will be acceptable if there is a notch. We will also allow for the diagnosis of glaucoma if the CDR differs by 0.3 or more between the two nerves.
6. Outcomes

Visual fields will be graded as normal, possible or probable glaucoma taking into account the GHT, PSD and pattern of visual field loss. Two graders will independently assess the visual fields and will adjudicate when in disagreement.

A final diagnosis of definite, probable, possible or no glaucoma will be made by the consensus of two independent reviewers. If they cannot agree, a third reviewer will be asked to evaluate the data and decide.

6.5.2 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. Pseudophakia and aphakia will be noted based on clinical examination. Such eyes will be excluded from cataract grading. The occurrence of cataract surgery and of YAG laser capsulotomy or surgical capsulotomy during follow-up will be noted. The occurrence also will be graded clinically at each study visit using a standardized grading system.

In pseudophakic 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).

6.5.3 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. Additional serious adverse ocular events will be noted through the adverse events reporting system.

6.6 Potential systemic complications of therapy

Systemic therapy with corticosteroids and/or immunosuppressive (corticosteroid-sparing) agents can be associated with adverse systemic side effects. Because the occurrence of systemic side effects with systemic therapy is an important element of the rationale for using fluocinolone acetonide implant therapy, detailed data will be collected on anticipated potential complications.

6.6.1 Potential complications of corticosteroid therapy

6.6.1.1 Hyperglycemia and diabetes mellitus

Fasting plasma glucose levels will be measured at baseline and annually thereafter. Casual plasma glucose levels will be measured at other study visits. 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]),

MUST Trial Protocol

MUST Protocol/MUSTProt_V2.4/Manall_2
2:13 pm Tuesday, July 5, 2005/rmj
hyperglycemia will be diagnosed when a fasting plasma glucose level which is above the normal limits of the assay but less than 126 mg/dL (7.0 mmol/L), or when a casual plasma glucose level is 140 mg/dL or higher but less than 200 mg/dL. Diabetic-level hyperglycemia will be diagnosed when a fasting plasma glucose level is 126 mg/dL or higher, or when a casual plasma glucose level greater than or equal to 200 mg/dL, both after confirmation by a repeat fasting plasma glucose level greater than or equal to 126 mg/dL. Treatment-induced diabetes mellitus will be diagnosed when a subject who is euglycemic at 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 study treatment) during follow-up; and/or 3) the subject was started on therapy for diabetes mellitus. The number of oral hypoglycemic medications and use of insulin at each visit will be applied to construct an ordinal scale evaluating the degree of difficulty in controlling diabetes mellitus: 0 = no hypoglycemic therapy; 1 = one oral hypoglycemic agent; 2 = 2 or more oral hypoglycemic agents; 3 = daily use of insulin. The baseline value on this scale will be subtracted from the maximum value of this scale during follow-up to indicate the change in glycemic status following randomization, allowing this outcome to be evaluated both in subjects who at baseline were non-diabetic and those who were diabetic but not requiring insulin.

6.6.1.2 Osteoporosis

Subjects will be screened at baseline and annually thereafter 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 to the setting of corticosteroid-induced bone loss, following the adaptation of the American College of Rheumatology, the MUST Trial will define osteopenia 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, likely to be infrequent during the follow-up period of the trial, also will be noted when confirmed by medical records.

6.6.1.3 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 at baseline and annually thereafter. 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), LDL levels will be ordinally 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.
6. Outcomes

6.6.1.4 Hypertension

Blood pressure (BP) measurement will be undertaken at all clinic 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. 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, 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.

6.6.1.5 Weight and height

Weight will be measured without shoes using a balance scale. Height without shoes will be measured to allow calculation of body mass index. Change in weight and in body mass index (in kg/m²) from baseline, and maximum values for these variables during follow-up will be evaluated.

6.6.1.6 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; 3) pancreatitis; and 4) ischemic necrosis of bone. Any additional serious adverse systemic events will be noted through the adverse events reporting system.

6.6.2 Potential systemic complications of other immunosuppressive therapy

Potent 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 during the trial are given below. These events, which would be extremely rare in the absence of immunosuppressive therapy, will be assumed not to be occurring in the implant group, unless noted on study blood draws or interval medical history forms.
6. Outcomes

6.6.2.1 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/μL or fewer, which corresponds to an infectious risk, and will serve as an indication for interruption of therapy in the MUST Trial. 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/μL or fewer, which will serve as an indication for suspension of therapy in the MUST Trial. 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.

6.6.2.2 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.

6.6.2.3 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.

6.6.2.4 Other systemic complications

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

6.7 Mortality

Mortality is not expected to occur at a high rate in this study, because neither uveitis nor the treatments being tested are thought to be associated with substantially increased risk of death. However, mortality will be evaluated in the trial for safety analyses. 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)
- two or more relatives or acquaintances testify that the participant has died

Survival audits will be performed annually and/or prior to publication of primary MUST Trial results. Date of death will be ascertained from the source reporting that death has occurred.

6.8 Adverse events reporting

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent any of the outcomes previously listed as a serious adverse event. When an investigator or clinical center staff member becomes aware of a SAE, it should be recorded on a Serious Adverse Event Report form and submitted to the CC within 3 working days after clinical center personnel become aware of the event, with follow-up reporting until the event has terminated. An assessment will be made by the clinical investigator at the managing clinical center as to whether the event is related to treatment. All serious events will be reported to the CC expeditiously regardless of the relationship to treatment (see MUST Trial Manual of Procedures). The CC will send copies of all SAEs to Bausch & Lomb, Inc. within 7 working days of their receipt at the CC. The CC will distribute reports of SAEs from one center to all other centers and to the DSMC (Data and Safety Monitoring Committee) in a timely fashion. The CC will notify the FDA of unexpected serious SAEs within 7 calendar days of receipt at the CC. All safety reports also will be distributed to clinical centers, the DSMB and the NIH project officers within 7 days.

6.9 Cost-effectiveness

6.9.1 Analytic Result

The goal of the cost-effectiveness analysis will be to determine if the differences in cost and effectiveness between fluocinolone implant therapy and oral corticosteroid therapy 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 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. While there are not absolute standards for what society is willing to pay for a quality adjusted life year or what is cost-effective, treatments are often considered cost-effective if they cost less than $50,000 to provide each additional QALY and not cost-effective if they cost more than $100,000 to provide each additional QALY. At levels of cost between $50,000 and $100,000 for each QALY gained treatments are not definitively labeled as being either cost-effective or not cost-effective. 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:

\[
\frac{\text{Cost(Implant)}-\text{Cost(Systemic)}}{\text{QALYs(Implant)}-\text{QALYs(Systemic)}}
\]

6.9.2 Effectiveness Measures

6.9.2.1 QALYs

The EuroQol and the SF-36 are instruments that can be used to generate QALYs. Historically, the EuroQol (in particular the EQ-5D) has been scored based on societal preferences for the 243 health states that the instrument can describe as expressed by a sample of individuals in the United Kingdom. There is current work under review that will allow the EQ-5D to be scored based on the preferences of survey respondents in the United States. While the SF-36 historically has been scored based on psychometric analysis rather than based on preference expression, there has been work to develop an algorithm (referred to as the SF-6D) that uses SF-36 data to generate a health state preference weight that can be used to calculate QALYs.

The EQ-5D will be gathered at baseline, three months, and three month intervals for the remainder of the study. The SF-36 will be gathered at baseline and every six months thereafter. This follow-up schedule will allow each study subject to accumulate as many as four quality adjusted life years.

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 3 months and at 9 months but not at 6 months) we can still assume a linear transition between the utility scores at 3 and 9 months. 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, particularly if both arms do not lose the same proportion of study subjects 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 24 month study period for patients 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. We can also explore whether the characteristics of individuals with missing data are systematically different from the characteristics of individuals with no missing data.

6.9.2.2 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.

6.9.3 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 a sufficient number 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 patients in the study.

6.9.4 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 patients in the study.

6.9.5 Discount Rate

While present value calculations will be relatively unimportant in the two to four year follow-up period for patients in the study, we will use a 3% discount rate. This discount rate may be important if we choose to look at any future costs of the ocular or systemic complications that may arise in this study but last much longer than the intended two to four year follow-up.

6.9.6 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 multiple 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.
7. Biostatistics

7.1 Sample size, power and detectable differences

The primary outcome for the MUST Trial is the eye-specific change in logMAR visual acuity from baseline to final follow-up, with analysis restricted to the eye(s) with uveitis that meet inclusion criteria at the time of randomization. A sample size of 200 patients in each group should have not less than 80% power to detect a difference between group means of 5 ETDRS letters, which is judged to be a clinically important difference. A difference in the mean change in visual acuity of 15 letters or more will be considered a clinically significant effect of treatment.

7.2 Statistical analysis

Principles for data analysis will include:

1) primary analyses of treatment effects will be by treatment assignment (intention-to-treat) to avoid selection biases;

2) data analysis will begin with exploration for patterns and for influential points, the accuracy of which will be evaluated and corrected if necessary;

3) “robust” statistical methods will be used when appropriate;

4) distributional assumptions will be checked, and transformations or non-parametric alternatives used if indicated;

5) simple regression analyses using treatment assignment as the covariate will be conducted, followed by multiple regression with stepwise model selection (including the set of covariates listed below as potential explanatory factors);

6) generalized estimating equations (GEE)\(^6\) will be used in regression models to account for excess correlation, when indicated, for:
   a) in longitudinal observations on the same patient; and
   b) (in “by eye” analyses) between eyes of the same patient. Some instances will require GEE accounting for two levels of clustering;

7) model checking will be performed as part of regression analyses, with inspection of residuals;
8) all key analyses will be replicated independently by different analysts.

Evaluation of visual acuity using a time-dependent "by eye" analysis, will be the primary efficacy analysis. This analysis will utilize a general linear model regression (GLM) with GEE to account for excess correlation when eyes and visits of the same patient are included. Alternative (sensitivity) analyses will be conducted, including a survival analysis approach.

In addition to treatment assignment, covariates to be considered as possible explanatory factors include:

1) anatomic location of uveitis (intermediate, posterior or panuveitis);
2) baseline clinical characteristics;
3) demographic factors; and
4) other variables potentially of predictive value, according to the judgment of the research group members conducting the analysis.

In addition to the primary analysis, visual acuity also will be evaluated as the proportion worse than 20/40 and the proportion legally blind (20/200 or worse and/or less than 20 degrees of visual field), both at the end of follow-up (GLM with GEE) and over time (logistic regression with GEE). Visual acuity outcomes also will be assessed from the "by patient" (worse eye) and "by patient" (better eye) perspectives.

Other analyses will be tailored to the nature of the secondary outcome data. Numerical (e.g., central macular thickness) and dichotomous data (e.g., presence versus absence of macular edema) will be analyzed by the general linear model. Ordinal data (e.g., grade of anterior chamber inflammation) will be analyzed using the proportional odds model. In instances where ordinal scales can be dichotomized in a meaningful way—e.g., anterior chamber inflammation inactive (grade 0 or trace) versus active (grade 1+ or higher)—ordinal data also may be dichotomized and analyzed using the general linear model. Survival time data (e.g., time-to-retinal detachment) will be analyzed using survival analysis. Where appropriate, Poisson regression will be used to compare event rates. The applicable generalized estimating equations methods to adjust for one level of excess correlation (between eyes of the same patient or between visits of the same patient) and for two levels of excess correlation (both between eyes of the same patient and between visits of the same patient) will be used as appropriate. Stepwise multiple regression analyses for secondary outcomes will evaluate a similar set of potential explanatory factors (covariates) in addition to treatment assignment as those evaluated for the primary analysis. Time-varying covariates will be used for analyses evaluating repeated measures of the outcome, if appropriate. Either "by eye" analyses (only evaluating eyes meeting inclusion criteria at baseline) or "by patient" analyses (better eye, worse eye), or both, will be conducted, depending on which analysis most rationally addresses the question of interest.
Standard errors of estimates from log-linear models will take account of possible overdispersion with respect to the assumed models. Robust variance estimation methods will be used whenever available.
8. Data and Safety Monitoring

Treatment effects monitoring, including formal interim analyses, will be conducted by a study Data and Safety Monitoring Committee (DSMC). This committee will consist of voting members and non-voting members (the Study Officers except for Dr. Kempen, who will be a treating physician in the study). Voting members will be appointed by the National Eye Institute; they will not be involved in the conduct of the MUST Trial, 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 twice per year, initially. The DSMC will be allowed to select its methods for monitoring the trial. 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.

Summaries of all adverse event data also will be reviewed by the DSMC at each meeting and will be submitted to appropriate IRBs. A DSMC Safety Officer will be appointed from among the physician voting members of the DSMC, who periodically will review summaries of all adverse event data prepared by the CC between DSMC meetings to make a determination as to whether the event is unexpected and possibly related to treatment.

Performance monitoring will include comparisons of enrollment, baseline variables, protocol deviations, and missing data between clinics. Clinic performance data will be presented at both DSMC and Steering Committee/Research Group meetings.
9. Patient rights and responsibilities

9.1 IRB approvals

This protocol will be submitted to the Institutional Review Board (IRB) of participating centers for review and approval. Clinics may not recruit patients into the MUST Trial prior to approval of this protocol by their governing IRB. All MUST Trial patients must sign a consent statement and medical record release form as well as HIPAA – complaint privacy practices acknowledgment prior to participation in the study.

9.2 Confidentiality of patient data

Confidentiality of patient 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 patient 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—may be disclosed, as needed, to collaborating MUST sites, the NEI, the FDA, and the pharmaceutical co-sponsor, as will be stated on a study privacy acknowledgment form signed by the participant at the time of enrollment. Also included in the privacy acknowledgment is the statement that representatives of NEI, FDA, the Institutional Review Boards, Coordinating Center and Bausch and Lomb, Inc. may see identifying information while reviewing study records. This privacy acknowledgment will be designed to conform with specifications of HIPAA regulations, and any other relevant regulations, as approved by the local governing authorities invested with oversight of HIPAA regulations at each participating site. Clinically relevant information from the study may be placed in the patient's medical record. Release of protected health information to any other persons or organizations will require additional written consent of the patient affected, except as required by law.
10. Biohazards

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.
Reference list


33. Bausch & Lomb 415-002 Study Group. A multicenter, randomized, controlled study to evaluate the safety and efficacy of an intravitreal fluocinolone acetonide (0.5 mg) implant compared to standardized therapy in patients with non infectious uveitis affecting the posterior segment of the eye. Amended Protocol. 12-26-2001. Tampa, FL, Bausch & Lomb, Inc. Ref Type: Pamphlet


MUST Trial Protocol

Reference list


Protocol Committee

Douglas A. Jabs, MD, MBA (Protocol Committee Chair, Study Chair)
John H. Kempen, MD, PhD (Protocol Manager, Study Vice-Chair)
Janet T. Holbrook, PhD (Coordinating Center Director)
Michael M. Altaweel, MD (Reading Center Director)
Matthew D. Davis, MD
C. Stephen Foster, MD
Gary N. Holland, MD
Glenn J. Jaffe, MD
Daniel F. Martin, MD
Curtis L. Meinert, PhD
Robert B. Nussenblatt, MD
James T. Rosenbaum, MD