The Adalimumab Vs. conventional ImmunoSupprEssion for uveitis (ADVISE) Trial

Statistical Analysis Plan (SAP)

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Contents

1.0 Glossary of Abbreviations

ADVISE	ADalimumab Vs. conventional ImmunoSupprEssion for uveitis
AE	Adverse Event
CC	Coordinating Center
CI	Confidence interval
DSMC	Data Safety and Monitoring Committee
EDTRS	Early Treatment Diabetic Retinopathy Study
EC	Executive Committee
EDA	Exploratory Data Analysis
EuroQual	Euro-Qual Questionnaire
FA	Fluorescein Angiography
GEE	Generalized Estimating Equations
HR	Hazard Ratio
LTFU	Lost to Follow-up
MTQAC	Medical Therapy Quality Assurance Committee
MUST	Multicenter Uveitis Steroid Treatment
NEI	National Eye Institute
OCT	Optical Coherence Tomography
OR	Odds Ratio
PHM	Proportional Hazards Model
RC	Reading Center
RG	Research Group
SAC	Statistical Analysis Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short-Form Survey
SITE	Systemic Immunosuppressive Therapy for Eye Diseases
VF	Visual Field
VFQ	Visual Function Questionnaire

2.0 Introduction

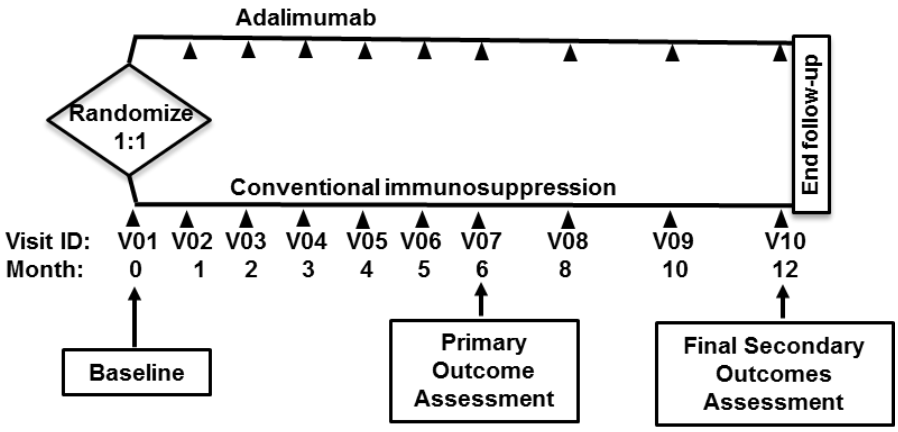
The goal of the Statistical Analysis Plan (SAP) is to describe the statistical plans for the statistical analyses of data collected in the ADalimumab Vs. conventional ImmunoSupprEssion for uveitis (ADVISE) Trial and comment on considerations that were incorporated into the plan. Areas covered include sample size estimates, exploratory data analysis (EDA), regression modeling, interim analyses, safety analyses, multiplicity, and missing data.

3.0 Study Overview

3.1 Study Design Synopsis

The proposed ADVISE Trial is a randomized, parallel-treatment, comparative effectiveness, clinical trial comparing adalimumab to conventional (small molecule) immunosuppression for the treatment of non-infectious, intermediate, posterior, or panuveitides (Figure 1). The primary hypothesis is that adalimumab will be superior to conventional immunosuppression for corticosteroid sparing, as determined by the proportion achieving inactive uveitis and prednisone ≤7.5 mg/day for 2 visits ≥28 days apart by 6 months of follow-up.

Figure 1. Trial Schema.



Eligible participants will be age 13 years or greater and have active or recently active (≤60 days) non-infectious, intermediate, posterior, or panuveitis for which immunosuppression is indicated. Participants should have either active uveitis requiring initiation of prednisone or an increase in dose to >7.5 mg/day or, if the uveitis is inactive, participants should be on a dose of prednisone >7.5 mg/day. Exclusion criteria include: 1) active tuberculosis; 2) untreated latent tuberculosis (e.g. positive interferon-γ release assay [IGRA] test, such as Quantiferon-gold; 3) Behçet disease (data suggest the Behçet disease does better with TNF-α blocking drugs[1,2]); 4) multiple sclerosis (TNF-α blockade may worsen multiple sclerosis); 5) brain magnetic resonance imaging (MRI) consistent with demyelinating disease (because individuals with intermediate uveitis are at an increased risk of multiple sclerosis[3,4], they will have an MRI imaged prior to enrollment); 6) a fluocinolone acetonide implant in either eye placed within 3 years of randomization; 7) use of anti-TNF monoclonal antibody therapy within 60 days prior to enrollment; 8) history of adalimumab intolerance or ineffectiveness; 9) current treatment with 2 immunosuppressive drugs, not including oral corticosteroids (most immunosuppressive drug regimens use a maximum of prednisone and 2 immunosuppressive drugs); and 10) pregnancy, lactation, or for women of child-bearing age, unwillingness to use appropriate contraception. Note that the Behçet disease and multiple sclerosis exclusions would have made only 4% of the participants in the Multicenter Uveitis Steroid Treatment (MUST) Trial ineligible for the ADVISE Trial. Hence the ADVISE Trial will enroll a population similar to that in the MUST Trial.

Participants will be followed every month for the first six months and then every two months thereafter. Table 1 shows the data collection schedule at each visit.

Table 1. Visit and Examination Schedule for the ADVISE Trial										
Month	**BL***	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**12**
Visit ID	**V01**	**V02**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08**	**V09**	**V10**
All patients										
Visual acuity†	X	X	X	X	X	X	X	X	X	X
Medical, ophthalmic, and treatment history	X	X	X	X	X	X	X	X	X	X
Weight and blood pressure	X	X	X	X	X	X	X	X	X	X
Eye examination	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography	X			X			X			X
Retinal color photos‡	X						X			X
Complete blood count & chemistry panel§	X	X	X	X	X	X	X	X	X	X
Quality of life (EuroQoL, SF-36, NEI-VFQ)	X			X			X			X
Disease-specific tests *Disease: Test(s)*										
Birdshot chorioretinitis: Visual field¶	X	X	X	X	X	X	X	X	X	X
Choroiditis (all types): FAF‖	X	X	X	X	X	X	X	X	X	X
Vogt-Koyangi-Harada: FAF and OCT	X	X	X	X	X	X	X	X	X	X
Retinal vasculitis and panuveitis with retinal vasculitis: FA#	X	X	X	X	X	X	X	X	X	X
Tests to identify exclusion characteristics prior to enrollment										
Interferon-γ release assay for tuberculosis (all patients)**	X									
MRI *for patients with intermediate uveitis only*††	X									
Pregnancy test for women of child bearing age	X									

* BL = baseline
† Evaluation of best corrected visual acuity after standard refraction
‡ 50 or 60˚ stereo photos of field 1-2 (disc and macula).
§ Including creatinine and liver enzymes
¶ Either Goldmann perimetry or automated perimetry with Humphrey SITA-fast 24-2 and P60 may be used, but once chosen, the visual field testing should be the same for all visit for each individual patient
‖ FAF= fundus autofluorescence.
FA = fluorescein angiography
** E.g. Quantiferon Gold
†† MRI = magnetic resonance imaging of the brain

3.2 Randomization and Stratification

Eligible participants will be randomized to receive adalimumab or conventional immunosuppression with a 1:1 allocation ratio. Randomization will be stratified by current immunosuppressive treatment for uveitis (1 or none)

and prednisone dose at randomization (< 30 vs ≥ 30 mg/day), i.e. a total of 4 strata, and implemented with a permuted block design with multiple block sizes. The randomization schedule will be produced in advance by the Coordinating Center (CC), and the randomization revealed via the ADVISE website after eligibility and stratum are confirmed.

3.3 Masking

Treatment administration will not be masked. Trial images will be uploaded to the Reading Center (RC) and evaluated there by graders masked as to treatment assignment. All other assessments will be made using unmasked examiners.

4.0 Outcomes

4.1 Primary Outcome

The primary outcome of the ADVISE Trial will be a corticosteroid-sparing treatment success, defined as inactive uveitis, on prednisone ≤7.5 mg/day for 2 consecutive visits ≥28 days apart within the first 6 months after randomization with individuals as the unit of analysis. The 2 consecutive visits ≥28 days apart was used in the SITE Cohort Study to avoid overestimation of benefits among participants who transiently achieve corticosteroid-sparing, but promptly relapse at the next visit. Since a minimum of two follow-up visits must occur prior to achieving a corticosteroid sparing success and prednisone must be tapered, the first outcome evaluation will occur at 2 months (V03) and will continue at every visit until the final study visit at 12 months (V10).

4.2 Secondary Outcomes

Secondary outcomes will include data collected at all follow-up visits, i.e. V02-V10, according to the collection schedule presented in Table 1.

- Secondary corticosteroid sparing outcomes:
  - Corticosteroid-sparing success: The ability to achieve inactive uveitis and prednisone ≤7.5 mg/day for 2 consecutive visits ≥28 days apart within one year of randomization
  - Prednisone discontinuation success: The ability to achieve inactive uveitis and discontinue prednisone for 2 consecutive visits ≥28 days apart within one year of randomization
  - Prednisone exposure (e.g. cumulative prednisone dose and/or mean prednisone dose) in the two groups through 1 year of follow-up.
- Best corrected visual acuity measured after a standardized refraction using logarithmic visual acuity charts
- Incidence of infections
  - Any infections requiring antimicrobial therapy
  - Tuberculosis (clinical diagnosis of tuberculosis)
  - Invasive fungal infections
  - Dermatomal or disseminated herpes zoster
- Macular edema measured using Optical Coherence Tomography (OCT)
- Quality of life (QoL) data collected at baseline, 3, 6, and 12 months
  - Health utility (EuroQoL 5-dimension [5D] and visual analog scales)
  - General health assessment (SF-36)
  - Vision related QoL (the 25-item National Eye Institute Visual Function Questionnaire [NEI-VFQ-25])
- Safety outcomes:
  - Systemic adverse events (e.g. cytopenias, elevated creatininte, elevated liver enzymes)
  - Serious adverse events (e.g. death, life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization)

5.0 Analysis Populations

The primary analyses will be based upon the 'as randomized' population, i.e. individuals will be included in the analysis according to their assigned treatment regardless of the actual treatment received, which follows the principle of intention to treat (ITT). A number of sensitivity analyses based upon the treatment received will be explored including but not limited to the following two examples. First, an 'as treated' analysis will incorporate individuals according to the current treatment received, which may change over time. Second, a 'per protocol' analysis will limit the analysis to the subset that received the assigned treatment according to the guidelines of the protocol throughout follow-up. Additional sensitivity analyses using causal inference techniques will be considered to address the issues of confounding and treatment by indication that arise from analyses based upon treatment received.

6.0 Statistical Analysis Methods

6.1 General principles

The primary analyses will include adjustment for randomization strata (immunotherapy use and prednisone dose). Additional analyses that are unadjusted or are adjusted for potential confounders will also be performed as secondary analyses. Robust standard errors will be computed using statistical program-based approaches when available and a bootstrap with the individual as the sampling unit when a pre-programmed approach is not available. All statements of statistical significance and confidence intervals will be based upon a 2-tailed test with a 0.05 level of significance, unless stated otherwise. Key analyses will be duplicated by a second statistician. All analyses will be performed using SAS version 9 or higher, STATA or R.

Prior to formal testing, exploratory data analyses including graphical techniques (e.g. histograms, scatter-plots, boxplots, spaghetti and lasagna plots) and summary statistics (e.g. median, IQR, proportion) will be used to examine cross-sectional and longitudinal patterns in the data as well as identifying potential violations of the assumptions underpinning formal testing, which can help guide decisions to apply transformations or alternative methods. In some cases, transformations of raw data have already been identified (e.g. log-transformation for retinal thickness and IOP) and will be implemented. Summaries will be made overall and by treatment group. During model selection and formal testing, graphical (e.g. residual plots) and analytic (e.g. tests of normality, proportional hazards assumptions) methods will be used to detect violations of modeling assumptions.

6.2 Sample Size

Sample size is calculated for the primary comparison of corticosteroid-sparing treatment success (inactive uveitis and prednisone $\leq$7.5 mg/day for 2 consecutive visits $\geq$28 days apart) at 6 months. Based on the preliminary data from the VISUAL III Study, we estimate that adalimumab will be successful in achieving the primary outcome in 75% of participants across all strata. The success of conventional small molecule immunosuppression varies according to the type and number of treatments. Based upon the Mount Sinai and MUST Trial data, we estimate that 75% of the participants will be in the stratum of no prior immunosuppression and 25% will be on one immunosuppressive agent at enrollment.[5] Based on the SITE data, the estimated success rate for antimetabolites is 55% and for calcineurin inhibitors 40%.[6-9] Participants in the no immunosuppression stratum will receive antimetabolites, whereas those in the one immunosuppression stratum will largely receive calcineurin inhibitors. Therefore, success rates of 55% and 40% are estimated for the no and one immunosuppressive agent strata, respectively. Based on the estimated stratum proportions and corresponding success rates, the overall conventional immunosuppression success rate is estimated to be 51%. In order to be conservative, we will assume a 10% loss to follow-up in each group and that all individuals were lost prior to observing a result. This is a conservative estimate since the loss to follow-up was 6% at 2 years in the MUST Trial.

Under these assumptions, a sample size of 222 (111 participants per treatment group) provides 90% power to detect significant differences between the 2 groups at 6 months if the underlying true proportions are 51% vs. 75% (46.1% vs. 67.5%, respectively, after adjusting for the loss to follow-up by assuming all of those lost did not achieve the corticosparing), assuming a two-sided type I error of 0.05. Prednisone discontinuation rates in VISUAL I and II were estimated to be 50%. Based upon data from Mount Sinai and the MUST Trial, estimates of prednisone discontinuation rates for standard immunotherapy range between 11%-35%. A sample size of 222 provides 80% power to detect an increase in the secondary outcome of discontinuing prednisone with inactive uveitis by 1 year from 30% to 50% (estimated from VISUAL I and II data), assuming a two-sided type I error of 0.05.

6.3 Primary outcome analysis

The primary goal of the trial is to establish whether adalimumab is superior to conventional immunosuppression for corticosteroid-sparing in the treatment of individuals with intermediate, posterior, or pannuveitis. The analysis will focus on the cumulative proportion with a success. Once a success has been achieved, then it will remain fixed for that individual thereafter. A more standard time to event analysis, which allows for censoring due to loss to follow-up, was considered. However, because the time required to taper prednisone to ≤ 7.5 mg/day depends substantially on the initial prednisone dose, small imbalances at baseline could influence greatly such analyses despite stratification. Therefore, time to event analyses will be used as sensitivity analyses. The 6-month time frame was chosen to allow sufficient time to observe the primary outcome regardless of the participant's prednisone dose at randomization and is likely to be more robust to imbalances. Multiple imputation will be used to address missing data due to missed interim visits and loss to follow-up.

Since a minimum of two follow-up visits must occur prior to achieving a corticosteroid success and prednisone must be tapered, the first outcome evaluation will occur at 2 months (V03) and will continue for every visit thereafter. Modeling will focus upon the period between 6 months and 1 year due to the potential for imbalances in the tapering patterns described above. Generalized estimating equations (GEE) will be used to fit logistic regression models comparing the two treatment groups over time while accounting for the correlation between replicate measurements. A saturated mean structure including visits starting at 6 months (V07-V10), treatment, and visit by treatment interaction terms plus the two stratification variables (baseline immunotherapy and initial prednisone dose) will be used. The mean model structure is:

$$logit(Y) = \beta_0 + \beta_1 A + \beta_2 P + \beta_3 S + \beta_4 V_7 + \beta_5 V_8 + \beta_6 V_9 + \beta_7 V_{10} + \beta_8 I_7 + \beta_9 I_8 + \beta_{10} I_9 + \beta_{11} I_{10}$$

where Y indicates the outcome (0: no corticosteroid sparing success, 1: corticosteroid sparing success), A indicates treatment (0: conventional immunosuppression, 1: adalimumab), P is an indicator of prednisone dose stratum (0: < 30mg/day, 1: ≥ 30 mg/day), S is an indicator of baseline immunotherapy stratum (0: none; 1: one), V_j is an indicator for visit j ($j \in 7, \ldots 10$), and I_j is an indicator for the visit by treatment interaction term for the j^{th} visit. An unstructured correlation matrix will be used to model the within-individual repeated measurements. Alternate correlation structures (e.g. exchangeable) will be explored if the unstructured covariance matrix is unstable. This model estimates the relative odds of corticosteroid-sparing for adalimumab vs conventional immunosuppression. The primary outcome will be represented by $exp(\beta_1 A + \beta_8 I_7)$, i.e. the odds ratio of the cumulative proportion for adalimumab vs conventional immunosuppression at six months (i.e. V07).

A standardized estimator, which allows for covariate adjustment, will be used to compare the absolute (as opposed to relative) difference in proportions at each time-point based upon the logistic model described above. This estimator has the advantage of providing a consistent estimate even if the means model is mis-specified.[10, 11] For each participant, the probability of a corticosteroid-sparing success at each time point is computed under two scenarios to create the counter-factual probabilities: (a) as if the participant had been assigned to adalimumab and (b) as if the participant had been assigned to conventional immunosuppression. Next, the average probabilities are computed for each group and the absolute treatment effect is calculated by taking the difference. The bootstrap will be used to calculate 95% confidence intervals and p-values. The equivalence margin is defined to be 5%.

Sensitivity analyses will be used to explore the alternate quantifications and robustness of the comparisons between the two groups. Longitudinal assessments of the components of corticosteroid sparing (activity and prednisone dose ≤ 7.5 mg/day) will be performed. In addition, time to event analyses will be used to assess the duration of success. Details of these modeling techniques are described in section 6.4. In addition, a variety of missing data techniques (Section 6.7) will be used to assess the potential impact of both interim missed visits and loss to follow-up.

6.4 Analysis of additional outcomes

The analyses of prednisone sparing success, an important secondary outcome, will be analyzed using the methods described for the primary outcome in Section 6.3 with the focus on the cumulative proportion at 1 year. Most of the remaining outcomes will be analyzed using longitudinal analysis techniques or event analysis techniques. Table 2 summarizes the outcome type and corresponding analysis technique for these outcomes with safety outcomes highlighted in italics. Additional details of safety monitoring are provided in Section 7.2.

Table 2. Summary of the type, modeling and frequency of secondary and safety outcomes for the ADVISE trial.
Safety outcomes are highlighted in italics. RZ = randomization; CI = confience interval; NLP = no light perception; LP = light perception.

Outcome Type	Modeling Techniques	Visit Intervals	ADVISE Outcomes
Continuous			
Person-level	GEE with a linear link Linear mixed effects models	V01-V10 V01, V04, V07, V12	Prednisone dose QoL outcomes (EQ-5D, SF-36, NEI-VFQ)
Eye-level	GEE with a linear link and bootstrap CIs Linear mixed effects models with a person-specific random intercept	V01-V10 V01, V04, V07, V12	Visual acuity Retinal thickness (log-scale)
Binary			
Person-level	GEE with a logistic link	V01-V10 V02-V10	Individual level activity (no activity in either eye) Prednisone dose ≤ 7.5 mg Prednisone halted
Eye-level	GEE with a logistic link and bootstrap CIs	V01-V10 V01, V04, V07, V12 V02-V10 V04, V07, V12	VA 20/40 or better VA worse than 20/200 Uveitis activity Macular edema (≥ 260μm) Improvement in macular edema Resolution of macular edema Worsening of macular edema
Event rates			
Person-level	Negative binomial regression	Real time post randomization	*Hospitalization* *Infections requiring antimicrobial therapy* *Type-specific infections* *SAEs*
Time to first event			
Person-level	Kaplan-Meier estimates Cox proportional hazards models	Real time post randomization V02-V10	*Death* *Hospitalization* *Infections requiring antimicrobial therapy* *Type-specific infections* SAEs *Other Systemic Events*
Eye-level	Frailty models	V02-V10 V04, V07, V12	*Decline in VA ≥ 6 lines or to NLP or LP* New onset macular edema

Evaluations of repeated binary outcomes (e.g activity, macular edema) and continuous outcomes (e.g. visual acuity) over time will be analyzed using generalized estimating equations (GEE) with Gaussian or logit links

that account for the nested correlations between observations over time and, for eye-specific outcomes, between eyes of the same participant.[12] A saturated mean structure including visit, treatment and visit by treatment interaction terms will be used. The visits that are included in the model depend upon the outcome (e.g. visual acuity V01-V10, corticosteroid sparing V07-V10) and are denoted in Table 2. An unstructured covariance matrix will be used to model the within-individual (or within-eye) repeated measurements. For eye-specific outcomes, the bootstrap will be used to compute standard errors, confidence intervals and p-values to adjust for between-eye correlation. Alternative correlation structures (e.g. exchangeable, AR(1)) will be explored if the unstructured covariance model is unstable

Events will be evaluated in two ways. Time to first event will be graphically explored using Kaplan-Meier curves and comparisons will be made using Cox proportional hazards models for individual outcomes (e.g. prednisone cessation) and frailty models for eye level outcomes (e.g. decline in VA $\geq$ 6 lines). Event rates and comparisons for repeated events (e.g. ocular corticosteroid injections) will be modeled using Negative binomial regression to account for over-dispersion and the model will include a random effect to account for between-eye correlation for eye-specific outcomes.[13]

An important safety consideration is cumulative prednisone exposure, which has been shown to be related to increased risks of cardiovascular disease and mortality. A variety of techniques will be used to monitor cumulative exposure. First, the longitudinal pattern of prednisone dose will be modeled using the techniques described above. Using these models, the population estimates of the cumulative dose over the lifetime of the trial will be computed by adding the dose estimates for each treatment group. Model-based estimates of 95% confidence intervals and treatment comparisons will be calculated. This method uses model-based approaches to adjust for missed visits and loss to follow-up. Alternately, multiple imputation will be used to 'fill in' the doses as the missed visits. Important factors in the imputation include, but are not limited to, prednisone dose at adjacent visits (given the rigorous nature of tapering regimes) and activity. Once the missing doses have been 'filled in' the cumulative usage can be calculated directly for each participant and standard analytic techniques can be used to compare the two treatment arms. Multiple iterations ensure that the analysis takes into account the uncertainty in the imputed values.

6.5 Subgroup analyses

In addition to gender, race, and ethnicity subgroup analyses, a number of planned subgroup analyses will be performed to assess the heterogeneity of the treatment effect. Of particular interest are the effects of the stratification factors: immunotherapy use at randomization (none vs one) and prednisone dose ($<$ 30 vs $\geq$ 30). Other planned subgroup analyses include age ($<$ 18 vs $\geq$ 18), clinic and baseline clinical characteristics including visual acuity (20/40 or better vs worse than 20/40) and macular edema (present vs absent). Depending upon recruitment, the assessment of clinic variability may be limited to regional and/or country level clustering; especially since treatment allocation is not stratified by clinic. Additional subgroups of interest that were not pre-planned may be identified during the course of the study. Such subgroups will be explored but the findings will be clearly labeled as unplanned explorations that are hypothesis generating in nature.

For exploratory purposes, the summary statistics and graphical techniques described above will be repeated within each subgroup to identify potential sources of heterogeneity. Tests of interaction (treatment effect x subgroup) will be used to evaluate whether or not there is significant heterogeneity between the groups defined by each subgroup. Subgroup analyses of clinical interest or with large differences in effect size that do not meet the strict criteria for significance ($p < 0.05$) may still be reported; however, they will clearly be labeled as not having met the criteria for establishing heterogeneity.

6.6 Multiplicity

When performing multiple hypothesis tests (as is the case here with the large number secondary outcomes), caution is needed when interpreting the results. Our primary focus for analyses of these outcomes will be on the parameter estimates and confidence intervals and overall consistency and interpretation of trial results as opposed to p-values as recommended by Wang et al.[14] Several methods of adjusting p-values for multiple comparisons exist; however, there is no clear consensus as to the most appropriate method available and it is difficult if not impossible to quantify the number of comparisons that will be performed ahead of time. In general, issuing cautions is sufficient along with calculating the expected number of false positives given the number of comparisons that were performed. For identifiable and related sets of outcomes (e.g. multiple assessments of macular edema or IOP), we will consider formal adjustments. Bonferroni adjustments assume that the tests are independent and therefore would be extremely conservative for outcomes that we would expect to be related. Therefore, we will estimate the covariance matrix for these related sets using a bootstrap approach and also estimate the null distribution of the minimum p-values for the multivariate distribution of z-scores using a global null hypothesis permutation distribution.

6.7 Missing data

For the primary outcome, multiple imputation will be used to address missing data due missed interim visits and loss to follow-up.[15] A variety of sensitivity analyses will be performed to determine the potential impact of missing data on our conclusions for the primary outcome as well as secondary outcomes. 'Best' and 'worst' case single imputation techniques will be implemented to define the range of impact. In addition, the effect size that would need to be observed in the missing data in order to change inference will be computed. For a more sophisticated approach, a variety of tools including but not limited to inverse probability weighting will be used.[16]

7.0 Trial Monitoring

An independent Data and Safety Monitoring Committee (DSMC) will be responsible for ongoing review of efficacy and safety data, policy and ethical issues, and study performance. The DSMC is composed of two ophthalmologists, one rheumatologist, two biostatisticians, and an ethicist. The current DSMC membership is listed in the DSMC Charter. Safety and efficacy monitoring, including formal interim analyses, will be performed by the CC and presented to the DSMC at regular DSMC meetings every 6 months with additional meetings as needed

7.1 Interim Efficacy Analysis

A single, formal, interim efficacy analysis will be performed once 40% of the participants have achieved 6 months of follow-up (i.e. evaluated for the primary outcome if not lost to follow-up or missing the visit), which is expected to occur when 67% of the participants have been recruited (estimated to be in the fourth quarter of year 3). We will employ an O'Brien-Flemming α-spending function in order to control the cumulative type I error rate for the primary outcome. The trial will be stopped for efficacy at the interim analysis if the p-value is <0.0008. The nominal type I error for the final analysis will be 0.0492. After adjusting for the interim analysis, we have 90% power (a loss of <1% from that described in Section 6.2) to detect an increase in the proportion of participants with treatment success from 51% to 75% (i.e. 46.1% vs. 67.5% after adjusting for 10% loss to follow-up) for conventional immunosuppression vs. adalimumab, assuming a 2-sided type I error of 0.0492. Additional efficacy analyses may be requested by the DSMC as needed during the course of the trial.

No stopping rules for futility will be implemented. However, if there is no significant difference between treatments at the end of the study, then we will assess whether adalimumab meets the criteria for non-inferiority as compared to standard immunotherapy using the pre-specified boundary of 5%, i.e. the lower boundary for the difference between the proportion with corticosteroid sparing at 6 months (adalimumab minus conventional) is greater than -5%.

7.2 Treatment and Assessment Monitoring

The CC will work with members of the MTQAC to ensure that the image evaluation and treatment guidelines are being followed at each clinic. Each month, the CC will identify discrepancies between the RC and clinic evaluation of disease-specific images as well as discrepancies between retreatment criteria and actual treatment received. For each individual with a discrepancy, a report including the images, treatment, and any additional data required by MTQAC to determine whether or not corrective action is required will be prepared by the CC and then forwarded to a representative of the MTQAC for review.

7.3 Safety Monitoring

Complications of uveitis and its treatment will be recorded on study data forms and submitted to the CC. Important serious or unusual medical events are reported to the CC within 7 days after clinical center personnel become aware of the event (see also Protocol section 7). An assessment will be made by the clinical investigator at the managing clinical center as to whether the event is related to treatment. These reports will be sent to the CC Safety Officer for immediate review and determination as to whether the event meets the criteria for a safety report and recommend whether expedited reporting to the DSMC, IRBs, or the FDA is needed. In addition, all events judged to be suspected unexpected serious adverse reactions will be reported as IND safety reports to the NEI project officer, the FDA, the pharmaceutical supplier (where appropriate), and all clinical centers in accordance with FDA regulations. The CC and clinical centers will submit all IND safety reports as expedited reports to their IRBs. Reports of important, serious or unusual medical events not deemed to be unexpected will be submitted as ad hoc, interim reports to the CC IRB, to the IRB of the clinical center in which the event was reported, as well as to any other study center IRBs which require such reports. Annual reports listing all reported adverse events will be submitted to the FDA as part of the annual IND report and to local IRBs as required.

Safety monitoring will be performed at every DSMC meeting. The DSMC will be provided with graphical and numeric summaries of the safety data (See Section 6), as well as formal statistical comparisons between the two treatment groups. Graphical and numeric summaries of efficacy outcomes without formal statistical testing will be provided to the DSMC at all meetings to allow sufficient information to adequately evaluate the risk benefit profile of the trial.

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