CLINICAL TRIAL PROTOCOL TITLE: DETERMINANTS OF MEDICAL AND SURGICAL TREATMENT OUTCOMES IN CHRONIC SINUSITIS

1. STUDY DESIGN:
   This study is a multi-institution, single-arm, non-randomized, longitudinal, observational, prospective cohort study. Study patients self-select endoscopic sinus surgery coupled with medical management as a subsequent treatment options for CRS. Study patients were randomized or assigned treatment for CRS in any way.

Inclusion criteria:
- Adult (≥ 18 years of age)
- CRS defined by 2007 Adult Sinusitis Guidelines.¹
- Provide written informed consent.
- Subject must be able to complete all study evaluations and HRQoL questionnaires written in English.
- Select subsequent treatment option to be dictated by the disease process and judgment and preferences of each study patient.
- Present to each enrollment site with a recent CT or previously established indications for a CT scan.
- Subjects will be counseled for continued medical management and surgical treatment options with each patient electing their preferred treatment option.

Exclusion criteria:
- Children (<18 years of age)
- Unable to complete questionnaires or clinical testing or cooperate with study evaluations in English.
- Unwilling to provide written, informed consent.
- Contra-indications for any type of continued medical therapy.
- Patients who have not undergone previous “maximum” prescribed medical therapy.

2. SUBJECT RECRUITMENT:
   All study subject recruitment will be centrally coordinated within the Oregon Sinus Center (OSC), a division of the Department of Otolaryngology – Head and Neck Surgery at Oregon Health & Science University in Portland, Oregon. The Center utilizes approximately 2550 square feet within the Center for Health and Healing (CHH) and is connected to the main OHSU campus via tramway. The Oregon Sinus Center is directed by Timothy L. Smith (PI/PD), MD, MPH, Professor and Chief of Rhinology, and provides state-of-the-art care for patients presenting with sinus problems. Patients are examined with modern equipment including 20 Storz Telecam DXII / Xenon Nova rigid, fiberoptic endoscope devices and a high resolution LCD monitor in each patient examination room. Approximately 300-350 endoscopic sinus surgery cases are performed on an out-patient basis at the CHH annually with a full medical support staff. Enrollment procedures will occur under the auspices of the clinical outcomes research program located within the clinical care setting of the Oregon Sinus Center. A full-time (1.0 FTE) Clinical Outcomes Program Coordinator (Mr. Jess Mace) is retained on site to facilitate and implement all clinical research activities, data collection, and patient follow-up. The Program Coordinator will independently contact patients after they are identified as potential study subjects by the clinicians and discuss the study with the emphasis that a patient’s treatment will in no way be affected by their decision to participate in this voluntary study. Written informed consent will be
obtained using documents approved by the Institutional Review Board at OHSU using Good Clinical Practice guidelines.²

Additional study subject recruitment will occur within Stanford Sinus Center, a division of the Department of Otolaryngology – Head and Neck Surgery at Stanford University Medical Center in Palo Alto, California (n=100), the Department of Otolaryngology – Head and Neck Surgery within the Medical University of South Carolina in Charleston, SC (n=488), the Department of Otolaryngology-Head and Neck Surgery within the University of Calgary (Rockyview General Hospital) in Calgary, Alberta, Canada (n=150), and the Department of Otolaryngology-Head and Neck Surgery at the University of Utah in Salt Lake City, Utah (n=150).

3. DATA COLLECTION:

A. Baseline Clinical Evaluation and HRQoL

Patient treatment is not be affected in any way by participation in this study. This is an on-going, observational study and no treatment or clinical testing per the standard of care will be altered as a result of enrollment. Patients who meet inclusion criteria, agree to participate, and provide informed written consent will be asked to provide a brief medical history, including demographic and comorbidity information including date of birth, race, ethnicity, gender, education level, household income, elected treatment, history of prior sinus surgery, insurance provider type, primary diagnosis, and comorbid conditions (Table 1). The enrolling physician will collect this information on standardized case report forms (CRFs). All patients will undergo baseline HRQoL assessment using the SinoNasal Outcome Test-22 (SNOT-22) Questionnaire, the Rhinosinusitis Disability Index (RSDI), and the Pittsburgh Sleep Quality Index (PSQI). The SNOT-22 is a validated, 22-item outcome measure applicable to both sinonasal conditions and surgical treatments (score range: 0-110). Derived from the SNOT-20, two additional questions were added to measure nasal blockage and sense of taste/smell. Lower total scores on the SNOT-22 imply better HRQoL.³ The RSDI is a 30-item, disease-specific survey instrument consisting of three subscales that evaluate the impact of CRS on a patient’s physical, functional, and emotional domain (total score range: 0-120).⁴ Higher RSDI scores indicate a greater impact of disease. The PSQI is an 18-item measure of sleep duration and quality during the previous 4 week period with higher scores (> 5) (total score range: 0-21) indicating worse sleep quality and/or domains. Scores are assessed using an openly available scoring algorithm.⁵ All survey evaluations will be

<table>
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<th>Table 1: DATA COLLECTION</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
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<tr>
<td>PSQI survey</td>
<td>X</td>
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</table>
administered by each Site Coordinator to study participants at baseline enrollment meetings. Survey time burden is minimized and is expected to require only 10-15 minutes.

B. Baseline Clinical Evaluation / Objective Testing

As per the standard of care, endoscopic evaluation will be completed at baseline using 2.7-4.0mm diameter 0-30º rigid endoscopes. The Lund-Kennedy standardized scoring system will be used to quantify bilateral, visual pathologic states within the region of the middle meatus including: nasal polyposis, mucosal discharge, edema, crusting, and scarring (score range: 0-20).\(^6\) Endoscopy exams will be completed using standard clinical endoscopic equipment (Karl Storz-Endoskope Telecom DXII & Xenon 175 light towers; KARL STORZ GmbH & Co., Tuttingen, Germany) per the standard of care during all clinical appointments.

When indicated a computed tomography (CT) scan of the paranasal sinuses, using 3.0mm contiguous images in the coronal plane to assess the degree of opacification in the maxillary, sphenoid, ethmoid, ostiomeatal complex, and frontal sinus regions, will be completed and reviewed at each initial clinic visit per the normal standard of care for CRS. All CT images will be scored by the enrolling physician using the Lund-Mackay scoring system (score range: 0-24).\(^7\)

For patients electing ESS as their treatment option, information about surgical procedures will be recorded by the enrolling physician/surgeon including unilateral or bilateral maxillary antrostomy, partial and/or total ethmoidectomy, sphenoidotomy, middle or inferior turbinate reduction, frontal sinus classifications, septoplasty, image guided surgery, and history of prior surgery (revision).

C. Outcome Assessments

No additional follow-up visits will be required outside of the standard of care, and CT and endoscopy exams will only be performed as part of the standard of care - all clinical testing will not be altered as a result of participating in the study at each enrollment site. All three follow-up clinic visitations observed during the study duration will be in accordance with the normal standard of care for treatment of CRS at each enrollment site. Research follow-up appointments at approximately 6 months, 12 months, and 18 months after enrollment will coincide with standard clinical appointments and will NOT be assigned during the study duration (Table I). Research appointment reminders will be given in the form of both written documentation and phone calls at least one day before each follow-up appointment by the Site Coordinator to remind patients of the additional time commitment after their standard clinical appointment. If subjects are unable to return for scheduled clinic visits, questionnaires along with self-addressed stamped envelopes, with be mailed to the participant. Follow-up phone calls and mailings are performed to ensure study compliance and minimal attrition.

The three main outcome measures to evaluate post-treatment changes in disease-specific HRQoL are the SNOT-22, RSDI, and the PSQI. Per the standard of care for post-treatment clinical visits for CRS, endoscopy exams will be scored using the same Lund-Kennedy scoring system. Post-treatment endoscopy will not be assigned for study purposes.

4. POWER / SAMPLE SIZE CALCULATION:

Sample size calculation was primarily based on the primary hypothesis and disease-specific QOL outcome measures (RSDI) for which we have pilot data. For the RSDI outcome, about 65% of patients in the medical treatment group are estimated to have a clinically significant improvement of 8 points score change, and a 10% absolute difference between the two groups is considered a clinically meaningful difference. To take into account the confounding variables in the logistic regression model, we assume the R\(^2\) between treatment
group and all other independent variables (e.g., obstructive sleep apnea, nasal polyposis, previous sinus surgery, comorbid anxiety) that would enter the model to be 0.15, a very conservative estimate. Based on these numbers, a total of 390 patients are needed to detect the 10% postoperative difference in the surgery groups with 80% power at the 0.05 significance level using a two-sided test.

Between all performance/enrollment sites, our goal is to recruit 488 patients with CRS so as to include final cohorts of 390 patients each with complete 18-month follow up. This 20% attrition rate is substantiated by preliminary data. For patients lost to follow up, there might be concern that they represent a different population compared to the patients who remain in the study. Analysis will be performed to determine if the patients lost to follow up have different pretreatment characteristics. In the unlikely event that substantially fewer patients complete the 18-month follow up, we will use the complete information available at 12 months to test the difference and construct the predictive models.

5. STATISTICAL ANALYSIS PLAN:

De-identified data was transferred from each enrollment center to a coordinating center (OHSU) for entry and storage into a central database (Microsoft Access; Microsoft Corp., Redmond, WA). Statistical analyses were completed using commercial software (SPSS v.22; IBM Corp., Armonk, NY). Participant characteristics, clinical measures of disease severity, and QOL survey measures were evaluated descriptively and data distribution normality was verified for all continuous measures. Final cohort data was dichotomized between participants with and without each comorbid characteristic to determine if each was a significant risk factor to postoperative improvement, including obstructive sleep (OSA) apnea for this particular investigation. Significant differences between participants with and without OSA were evaluated using 2-tailed sample t-tests, Mann Whitney-U tests, and chi-square (χ²) testing. Matched pairing t-tests or Wilcoxon signed rank tests were used to evaluate significant differences over time. The primary outcomes of interest include the postoperative improvement in mean endoscopy and QOL survey scores; operationalized by subtracting preoperative scores from last available postoperative scores. Improvement in the percentage of poor sleep was determined using McNemar’s paired sample χ² test.

Simple stepwise linear regression was used to identify significant independent risk factors associated with significantly different mean postoperative improvement. Preliminary models included a binary measure of OSA at the main exposure variable of interest and all independent factors screened for univariate significance (p<0.250) while adjusting for potential enrollment site differences. Twenty-four variables were additionally screened for univariate significance including baseline characteristics and descriptors of surgical extent. Without adjustment for preoperative scores final models used a manual forward selection (p<0.100) and backwards elimination (p<0.050) process and multi-collinearity was evaluated using variance inflation factors (VIFs). Unadjusted and adjusted regression coefficients (β), standard errors (SE), 95% confidence intervals, and estimates of type-I error (p-values) are reported. The percentage of final model variance was evaluated using coefficients of multiple determination (R²).

6. ANTICIPATION OF RISK AND PRECAUTIONARY MEASURES:

We anticipate minimum risk associated with all research protocols for this multi-institution observational study. There is only minimal deviation from the normal standard of care for surgically treated CRS. If at any point during the study it has been determined that an
adverse event (AE) or a serious AE has occurred, directly related to the study protocol, the necessary reporting will take place and termination of the study will be considered.

7. PROTECTION OF PRIVACY AND CONFIDENTIALITY:
   All collected study data will be kept in a separate storage area, appropriately labeled for the study in the Oregon Sinus Center at OHSU. This storage area and any additional study materials will be kept in a secured office with a locking door. Only certified study personnel will have access to this data. The appropriate data safety monitoring plan will be established at OHSU in accordance with guidelines developed by the Institutional Review Board (IRB). Data monitoring will be initiated by the investigator through internal reviews by both the Study Coordinator and PI. Patient confidentiality will be assured through the use of assigning unique study numbers and initials on all CRFs at all enrollment sites, as well as closed enrollment meetings during normal clinical hours. All CRF’s will be developed and controlled by the PI and are available to the IRB at any time. Quality of life survey and clinical data hardcopies will be photocopied with unique study ID (no PHI) and transferred from each enrollment site to the Coordinating Center at OHSU through the United States Postal Service using a secure envelop. Published results will not include any protected health information. Written informed consent will be obtained using forms approved by the IRB at OHSU.

   All data entered into a database for subsequent statistical analysis will be completely de-identified using unique study identification numbers. Databases will be kept under a password protected desktop computer managed by the OHSU Study Coordinator.

8. ANTICIPATED BENEFITS ASSOCIATED WITH THE STUDY PROTOCOL:
   Study participants may or may not benefit directly from baseline research evaluations and regularly monitored follow-up visits. Patients and insurance companies will be charged for all standard procedures associated with the baseline evaluation and follow-up visits considered to be within the normal standard of care.

   We hope that this investigation may improve our understanding of the clinical benefit, natural history, and comparative treatment effectiveness for recalcitrant CRS. The results may assist in directing future CRS studies towards finding optimal HRQoL and therapeutic outcomes so patients may be treated more effectively.

9. DATA SAFETY MONITORING:
   There is no formal data safety monitoring board in place for this study apart from the members of the research team. Patients and data derived from this study will be monitored according to the OHSU Data Safety Monitoring Plan associated with this protocol.
REFERENCES:


