**STUDY PROTOCOL**

**Project Title**: The Impact Of The Addition Of Budesonide To Low-Pressure, High-Volume Saline Sinus Irrigation For Chronic Rhinosinusitis

**Short Title**: Neti-Cort Study

**Estimated Start Date:** December 1, 2015

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**Abstract**

Chronic rhinosinusitis (CRS) is a condition characterized by inflammation of the paranasal sinuses and lining of the nasal cavity for 12 weeks or more. The characteristic symptoms of rhinosinusitis include facial pain-pressure-fullness, and nasal discharge accompanied by nasal obstruction. Rhinosinusitis is exceedingly common and estimates suggest that 1 in 8 adults are affected and over 30 million cases are diagnosed each year. Analysis of national ambulatory data demonstrates that rhinosinusitis accounts for more outpatient antibiotic prescriptions than any other diagnosis.

CRS is primarily an inflammatory disease, with occasional exacerbations associated with infection. Treating the episodic infections alone leaves the underlying condition untreated, likely contributing to an increased frequency of exacerbations. CRS is associated with sinus edema and impaired mucociliary clearance. With edema-related obstruction and retained mucus, bacterial infection can more easily occur.

Nasal sinus saline irrigation (aka Neti-Pot) is widely recommended and is a common treatment for CRS. The use of either isotonic ("normal" saline) or hypertonic saline is recommended and exact recommendations for amount of volume vary substantially. There have been over 12 studies (10 RCTs, 1 systematic review, and 1 meta-analysis) examining the impact of saline irrigation in the management of CRS. Both of the reviews concluded that nasal saline irrigation is an effective treatment for CRS with a high benefit to risk margin. Nasal saline irrigation is low-cost, has an excellent safety profile, and has high patient acceptance, which make it an appealing long-term topical treatment strategy.

Budesonide is an anti-inflammatory glucocorticoid steroid that is used for a variety of common ailments. Among conditions related to the respiratory tract, budesonide is used as an inhalational drug for the treatment of asthma, COPD, allergic rhinitis, and nasal polyps. Three studies examined the use of topical budesonide delivered through low-pressure, high-volume saline irrigation. All three studies reported dramatic improvement in symptoms with minimal local or systematic effects.

The **goal of this research project** is to explore the impact of the addition of budesonide to high-volume, low-pressure nasal sinus saline irrigation (aka “Neti-Pot”-type systems) for patients with chronic rhinosinusitis with or without nasal polyps.

The **specific aims** of this study are as follows:
1. To determine the incremental benefit of the addition of budesonide to nasal irrigation for CRS patients.
2. To describe the adverse effects related to budesonide nasal saline irrigation.

To answer the research question, the study design will be a double-blind placebo-controlled randomized clinical trial. Up to 80 adult patients with complaints of purulent (not clear) nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both and reduction or loss of smell for 12 weeks or greater will be eligible. The intervention will be 4 weeks of budesonide powder added to saline rinse or lactose placebo added to saline rinse alone. The primary outcome measure will be the average per-patient change in the SNOT-22 between the two treatment groups.

**SYNOPSIS**

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| **Study Title** | The Impact Of The Addition Of Budesonide To Low-Pressure, High-Volume Saline Sinus Irrigation For Chronic Rhinosinusitis |
| **Objective** | The objective of this research project is to explore the impact of the addition of budesonide to low-pressure, high-volume saline nasal irrigation ("Neti-Pot") for patients with chronic rhinosinusitis with or without nasal polyps. |
| **Study Period** | Planned enrollment duration for each subject: 1 month<br>Planned study duration: I year |
| **Number of Patients** | Up to 80 adult patients with complaints of purulent (not clear) nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both and reduction or loss of smell for 12 weeks or greater. |
| **Study Drug** | Budesonide and identical appearing placebo containing lactose. Budesonide is an anti-inflammatory glucocorticoid steroid that is used for a variety of common ailments. |
| **Study Design** | Prospective, double-blind, placebo-controlled randomized clinical trial |
| **Inclusion and Exclusion Criteria** | *Inclusion Criteria:*<br>Twelve (12) weeks or longer of two or more of the following signs and symptom consistent with chronic rhinosinusitis (CRS)[1, 2]:<br>• mucopurulent drainage (anterior, posterior, or both), nasal obstruction (congestion),facial pain-pressure-fullness, and decreased sense of smell<br><br>AND inflammation documented by one or more of the following findings:<br><br>• purulent (not clear) mucus or edema in the middle meatus or ethmoid region,<br>• polyps in nasal cavity or the middle meatus, and/or<br>• radiographic imaging showing inflammation of the paranasal sinuses<br><br>*Exclusion criteria:*<br>• Unable to speak English<br>• History of comorbid ciliary dyskinesia, cystic fibrosis or any other mucociliary condition<br>• Dependence on prolonged corticosteroid therapy for comorbid conditions, such as asthma and chronic obstructive pulmonary disease.<br>• History of oral or systematic antibiotic use in the past 2 weeks<br>• History of nasal or sinus surgery within past 6 weeks<br>• History of cerebrospinal fluid leak<br>• History of allergy to budesonide or other topical steroids<br>• Pregnant or breast feeding<br>• Current infection or history of one of the following infections: Tuberculosis (TB) lung infection, or Herpes infection of the eye.<br>• Baseline SNOT-22 total scores below 9 were excluded due to the inability to achieve a minimally clinically improved difference<br>• Known history of bleeding disorder, topical or injectable lidocaine allergy, use of blood thinners |

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|---|---|
| **Primary Outcome** | The change in the SNOT-22 (©2006, Washington University, St. Louis, MO) score between baseline and four-week intervention and calculated as: $\Delta$SNOT-22 = SNOT-22$_{\text{baseline}}$ — SNOT-22$_{\text{4-week follow-up}}$. |
| **Measurements** | 1. SNOT-22<br>2. ACE-27 Comorbidity Index<br>3. Lund Kennedy Endoscopy Grading Scale<br>4. Lund – MacKay CT score (not required)<br>5. Global Clinical Impression Scale |
| **Statistical Methodology** | Within subject change in SNOT-22 between intervention groups. Sub-group analyses will be performed for patients with and without polyps and prior history of sinus surgery |

**Statement of the Research Problem**

**Definition and Burden of Rhinosinusitis**

Chronic rhinosinusitis (CRS) is a condition characterized by inflammation of the paranasal sinuses and lining of the nasal cavity for 12 weeks or more.[3] The characteristic symptoms of rhinosinusitis include facial pain-pressure-fullness, and nasal discharge accompanied by nasal obstruction. Rhinosinusitis is exceedingly common and estimates suggest that 1 in 8 adults are affected and over 30 million cases are diagnosed each year.[4, 5] Analysis of national ambulatory data demonstrates that rhinosinusitis accounts for more outpatient antibiotic prescriptions than any other diagnosis.[6] Patients with CRS visit primary care clinicians twice as often as those without the disorder and have 5 times as many prescriptions filled.[7]. A survey performed in 2007 found that approximately $8.3 billion is spent annually on CRS, primarily on prescription drugs and office-based care.[8] Surgery, which costs on average $7,700 per patient, is performed nearly 250,000 times per year in the United States[9] In September 2005, the balloon sinuplasty device received FDA approval as the first catheter-based system for dilation of the paranasal sinuses. This minimally invasive procedure has caught the attention of the media and the public and its rate of adoption within the otolaryngology community has been rapid, albeit with controversy surrounding its indications and outcomes.

CRS is primarily an inflammatory disease, with occasional exacerbations associated with infection. Treating the episodic infections alone leaves the underlying condition untreated, likely contributing to an increased frequency of exacerbations. In this way, CRS is very similar to chronic bronchitis. CRS is associated with sinus edema and impaired mucociliary clearance. With edema-related obstruction and retained mucus, bacterial infection can more easily occur.[10]

Mucus hypersecretion is a hallmark of chronic rhinosinusitis (CRS) and is associated with several common symptoms. Mucin 5AC (MUC5AC) is a major respiratory mucin gene that codes for a gel-forming mucin glycoprotein found in the gastric and respiratory epithelia. MUC5AC is overexpressed in CRS patients both with and without nasal polyps.[1-6] Furthermore, CRS is associated with changes in nasal epithelial tissue, including epithelial damage and an increase in basement membrane thickness.[7-9]

**Medical Management**

The medical management of CRS includes antibiotics, topical nasal steroid sprays, saline irrigation. Antibiotics are often prescribed for CRS and national surveys suggest a large degree of over utilization with development of serious adverse side effects and resistant organisms.[11-24]

**Nasal Sinus Irrigation**

Nasal sinus saline irrigation (aka Neti-Pot) is widely recommended and is a common treatment for CRS. The use of either isotonic ("normal" saline) or hypertonic saline is recommended and exact recommendations for amount of volume vary substantially. There have been over 12 studies (10 RCTs, 1 systematic review, and 1 meta-analysis) examining the impact of saline irrigation in the management of

CRS. Of these 12 studies one was a systematic review and the other was a meta-analysis[18, 25] Both studies concluded that nasal saline irrigation is an effective treatment for CRS with a high benefit to risk margin. Nasal saline irrigation is low-cost, excellent safety profile, and high patient acceptance make it an appealing long-term topical treatment strategy.[26]

**Topical Nasal Steroid Spray**

The impact of intranasal corticosteroid sprays (INCS) in patients with CRS without polyps was explored with two high quality systematic reviews. In the first published in 2009, Kalish et al.[27] reviewed 424 potential studies and only nine randomized trials involving 657 patients were eligible. Of these nine studies, only 5 were acceptable for further inclusion. The summary estimate for overall response to treatment showed no significant benefit and substantial variability among studies (5 trials: RR 0.75, 95% CI 0.50-1.10, P = 0.14, chi(2) = 13.78, I(2) = 66.2%). Total symptom score was reported in three trials with a standardized mean difference favoring topical steroids. The authors concluded that there is insufficient evidence to demonstrate a clear overall benefit for topical steroids in CRS without polyps; however, their use appears safe and may show some symptomatic benefit. Snidvongs et al.[28] published a Cochrane Review in 2011 that combined 5 trials reporting symptom scores. When compared to placebo, topical steroid improved symptom scores (standardised mean difference -0.37; 95% confidence interval (CI) -0.60 to -0.13, P = 0.002; five trials, n = 286) and had a greater proportion of responders (risk ratio 1.69; 95% CI 1.21 to 2.37, P = 0.002; four trials, n = 263). The authors' concluded that topical steroid is a beneficial treatment for CRS without polyps and the adverse effects are minor. The authors also concluded that direct topical delivery of steroid to the sinuses may bring more beneficial effect than simple nasal delivery and that further studies comparing different topical drug delivery methods to the sinuses are warranted.

While the use of INCS is generally recommended in the setting of CRS, there is evidence of the limited penetration of the steroid beyond the nasal cavity and into the paranasal sinuses[29, 30]. Therefore, there has been great interest in the use of novel delivery approaches and devices to improve intra-sinus corticosteroid deposition.[31]

**Non-Standard Delivery of Topical Steroids**

Three studies examined the use of topical steroids delivered through low-pressure, high-volume saline irrigation. Snidvongs et al. [32] published a prospective cohort of 111 patients, 49 of whom had a diagnosis of CRS without nasal polyps. Treatment was with once daily nasal irrigations of 1mg budesonide/betamethasone in 240 ml of normal saline in the immediate post-operative period. Significant improvements were seen in SNOT-20 scores (2.3 +/- 1.1 vs 1.2 +/- 0.9), symptom scores (2.5 +/- 1.1 vs 1.4 +/- 1.0) and Lund-Kennedy endoscopy scores (4.3 +/- 2.0 vs 1.9 +/- 1.6). No adverse outcome analysis was reported. Another study, completed by the PI and colleagues at Washington University[33], was an open-label prospective study enrolling 9 subjects. Subjects received a 30 day course

of 250 µg budesonide diluted into 5 mL of isotonic saline and delivered into each nostril QID. Subjects also underwent adrenal function assessment with the cosyntropin test before and after budesonide therapy. All subjects showed adequate adrenal response to cosyntropin stimulation before and after the budesonide trial and the mean change in SNOT-20 scores before and after budesonide therapy was statistically and clinically improved. Steinke[34] conducted a prospective pilot study in 8 subjects with allergy as defined by a positive skin prick test and 4 subjects were classified as having aspirin-exacerbated respiratory disease, and all but 1 had physician-diagnosed asthma. The subjects received a 3-month course of twice daily budesonide irrigations (500 µg into >100 ml saline). The median sinus CT score before treatment was 15 (maximum, 30), which improved to 5 ($P < .05$) after treatment. Based on a visual analog scale, the authors we calculated scores for each of 16 sinus symptoms on a scale of 0 to 6, with 6 being severe and 0 none (maximum, 96). After budesonide treatment, subjects' sinus scores decreased (mean ± SD) from 43.1 ± 5.4 to 20.1 ±3.0 ($P<.02$). In addition, subjects reported a significant improvement in sense of smell. Of the four patients with nasal polyps, three had complete resolution. The authors concluded that their study supports the concept that addition of budesonide inhalation suspension to standard nasal saline irrigation produces subjective and objective benefit in eosinophilic sinus disease and that a double-blind, placebo-controlled study of budesonide inhalation suspension in nasal saline washes for patients with CRS was warranted.

**Specific Aims**

The **goal of this research project** is to explore the impact of the addition of budesonide to low-pressure, high-volume nasal sinus saline irrigation (aka "Neti-Pot") for patients with chronic rhinosinusitis with or without nasal polyps.

The **Specific Aims** of this study are as follows:

**1. To determine the incremental benefit of the addition of budesonide to nasal irrigation for CRS patients.**

Hypothesis: Budesonide is a topical corticosteroid with potent anti-inflammatory properties and when delivered via nasal saline irrigation will be more effective than normal saline alone in the treatment of symptoms associated with chronic rhinosinusitis. To evaluate this hypothesis a double-blind randomized clinical trial will be performed among adult subjects presenting to Washington University Department of Otolaryngology-Head and Neck Surgery for the treatment of chronic rhinosinusitis. The primary outcome measure will be the within subject change in SNOT-22 scores among subjects in the two arms of the study after four weeks of daily low-pressure, high volume sinus irrigation containing either isotonic saline and budesonide or isotonic saline alone.

**2. To describe the adverse effects related to budesonide nasal saline irrigation.**

Subjects will be queried regarding adverse events experienced during participation in the study and a determination of the likely association with budesonide will be made.

**Experimental Plan, Methods, and Data Analysis**

**Study Design**

Double-blind placebo-controlled randomized clinical trial

**Subjects**

Up to 80 adult patients with complaints of purulent (not clear) nasal drainage accompanied by nasal obstruction, facial pain-pressure-fullness, or both and reduction or loss of smell for 12 weeks or greater.

*Inclusion Criteria:*

Twelve (12) weeks or longer of two or more of the following signs and symptom consistent with chronic rhinosinusitis (CRS)[1, 2]:

- mucopurulent drainage (anterior, posterior, or both), nasal obstruction (congestion),facial pain-pressure-fullness, and decreased sense of smell

  AND inflammation documented by one or more of the following findings:

- purulent (not clear) mucus or edema in the middle meatus or ethmoid region,
- polyps in nasal cavity or the middle meatus, and/or
- radiographic imaging showing inflammation of the paranasal sinuses

*Exclusion criteria:*

- Unable to speak English
- History of comorbid ciliary dyskinesia, cystic fibrosis or any other mucociliary condition
- Dependence on prolonged corticosteroid therapy for comorbid condition, such as asthma and chronic obstructive pulmonary disease.
- History of oral or systematic antibiotic use in the past 2 weeks
- History of nasal or sinus surgery within past 6 weeks
- History of cerebrospinal fluid leak
- History of allergy to budesonide or other topical steroids
- Pregnant or breast feeding
- Current infection or history of one of the following infections: Tuberculosis (TB) lung infection, or Herpes infection of the eye.
- Baseline SNOT-22 total scores below 9 were excluded due to the inability to achieve a minimally clinically improved difference

**Variables of Interest**

**Demographic** - age, gender, and race.

**Index condition** – Duration of CRS symptoms, response to previous treatments

**Co-morbid conditions** - Presence and severity of general comorbid conditions will be assessed with ACE-27.[35] Presence of rhinosinusitis-specific comorbidities will include: inhalant allergies, asthma, and aspirin sensitivity

**Previous sinus and/or nasal surgery** - Previous sinus and/or nasal surgery, including functional endoscopic sinus surgery, turbinate reduction, and septoplasty will be captured and duration since surgery to time of enrollment.

**Randomization**

The study statistician, Dr. Dorina Kallogjeri, will use a randomized block design for study drug assignment.

**Intervention**

The study intervention will be budesonide powder (0.5 mg/capsule) or an identical-appearing placebo product containing lactose. All subjects will be provided with the 8-ounce (240 ml) NeilMed Sinus Rinse Regular Bottle Kit and a one-month supply of USP Grade Sodium Chloride & Sodium Bicarbonate Mixture (pH balanced, Isotonic & Preservative & Iodine Free) commercially prepared packettes. Subjects may substitute the NeilMed Sinus Rinse Regular Bottle Kit for a nasal irrigation system, which in the opinion of the Principal Investigator, is similar to the NeilMed system and embodies the low-pressure, high-volume concept of nasal irrigation. Examples of such systems include, but are not limited to, ceramic or plastic neti pot or nasal douch (Nasendusche). Subjects will need to purchase distilled water or boil tap water for five minutes for use with the saline irrigation. Subjects will be required to dissolve the contents of two capsules into the 8-ounce (240 ml) NeilMed Sinus Rinse Regular Bottle along with the saline rinse. All subjects will be instructed to irrigate both right and left nasal cavity with one-half of the contents of the nasal rinse once daily. The subjects will receive written instructions and a video prior to initiation of the intervention to ensure proper delivery.

Each study bottle will contain 60 capsules of Budesonide or placebo and will be assigned with a number from 1-80. Only Dr. Kallogjeri (biostatistician) will have a list that links the treatment type (Budesonide or placebo) with the bottle number. The bottle number will correspond to the randomization schedule provided from Dr. Kallogjeri. The subject and the rest of the study team will remain blinded to the randomization assignment. The subject and the rest of the study team will only know what bottle number is being assigned, not which treatment is contained in each bottle. Dr. Kallogjeri is the biostatistician of the study and otherwise is not involved with the participants.

In the event of a Serious Adverse Event determined by the PI to necessitate the breaking of the blind, the intervention assignment will be revealed by Dr. Kallogjeri to the medical staff doctor caring for the

patient. In the event Dr. Kallogjeri is unable to be reached in a time needed, to assure the safety of the subject, the blind can be broken by Sara Kukuljan, RN, or Drs. Piccirillo or Schneider and information will be shared with the medical staff assuming care for the patient.

The active drug and placebo will be prepared by Genesis Pharmacy, St. Louis Missouri and delivered to the Clinical Outcomes Office where the products will be stored in a locked cabinet. The cost of sufficient budesonide for the study duration (i.e., 60 budesonide capsules) will be $75 and the cost of sufficient quantity of lactose capsules will be $25.

**Budesonide**

Budesonide is an anti-inflammatory glucocorticoid steroid that is used for a variety of common ailments. Among conditions related to the respiratory tract, budesonide is used as an inhalational drug for the treatment of asthma, COPD, allergic rhinitis, and nasal polyps. The mechanism of action of budesonide is similar to other corticosteroids and includes a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation.(AstraZeneca 2000 2000)

Subjects randomized to the budesonide intervention arm will be required to mix 1.0 mg (provided as two capsules containing 0.5 mg budesonide each) budesonide into the sinus rinse bottle and rinse each nasal cavity with one half of the bottle (~ 4 ounces or ~120 ml) daily. The inert ingredients are: loxasperse powder, which increases solubility and dispersibility of budesonide and is microbiologically safe; mannitol, which is widely used in pharmaceutical products as a capsule diluent; and Xylifos™ powder, which is a proprietary powder excipient used safely in pharmaceutical compounding for nasal nebulization or nasal irrigation.

**Exemption From IND Requirements**

The use of budesonide in a nasal saline rinse is a change in the approved route of administration. An exemption from IND requirements will be requested as the proposed use of budesonide in this study fulfills all of the criteria for exemption.

1. Budesonide is lawfully marketed in the United States.
2. This study is not intended to be reported to the FDA in support of a new indication or significant change in labeling.
3. This study is not intended to support a significant change in the advertising for the drug.
4. The study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of budesonide.
5. The study will be conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The study is not intended to promote or commercialize budesonide.

**Placebo**

The placebo product will contain lactose monohydrate and will be supplied in clear plastic capsules, which are identical to the budesonide capsules. The lactose capsule will only contain lactose as there are no other ingredients.

**Concomitant Medications**

At the time of enrollment, most subjects will be expected to already be using topical nasal steroid medication (ie., fluticasone or Flonase®). Subjects currently using a topical nasal steroid spray will be asked to continue this medication. Subjects not currently using a topical steroid spray will be asked to initiate therapy, unless there is a contraindication or personal reason for not wishing to use. Topical nasal steroid sprays are indicated therapy for CRS and not considered experimental.

**Patient-reported Outcome Measure**

The SNOT-22 (©2006, Washington University, St. Louis, MO) will be used to capture the physical, functional, and emotional consequences of rhinosinusitis. The SNOT-22 is a validated, patient-reported outcome measure applicable to chronic sinonasal conditions.[36] The severity of 22 rhinosinusitis-related symptoms and physical signs are measured using a Likert scale as follows: 0= "*No problem*"; 1="*Very mild problem*"; 2="*Mild or slight problem*"; 3="*Moderate problem*"; 4="*Severe problem*"; and 5="*Problem as bad as it can be*". Higher total scores on the SNOT-22 suggest worse patient functioning or symptom severity (score range: 0-110). A minimally clinically improved difference (MCID) in symptoms that is perceptible and pertinent to the individual patient on the SNOT-22 has been previously described as an improvement of at least 8.9 points.[37, 38]

**Primary Outcome Measure**

Study participants will be asked to complete the SNOT-22 at baseline, two weeks, and four weeks. The change in SNOT-22 scores between baseline and four weeks will serve as the primary outcome measure in this study and will be calculated as:

$$\text{Primary Outcome Measure, } \triangle\text{SNOT-22} = \text{SNOT-22}_{\text{baseline}} - \text{SNOT-22}_{\text{4-week follow-up}}.$$

To assess the trajectory of change within subjects randomized to the two treatment arms the baseline, two-week, and four-week SNOT-22 assessment will be compared.

**Secondary Outcome Measure.**

The overall response to treatment will be measured with a modification of the Clinical Global Impression (CGI) scale.[39] Upon completion of the study, subjects will be asked to answer the following question: "*Overall, how would you rate your response to treatment*?" Response options are: 1 = *Very Much Improved*, 2 = *Much Improved*, 3 = *Minimally Improved*, 4 = *No Change*, 5 = *Minimally Worse*, 6 = *Much Worse*, 7 = *Very Much Worse*.

**Physical Examination**

A directed physical examination, consisting of examination of the nasal cavity with a 0-degree rigid nasal endoscope, will be performed by a board-certified otolaryngologist after application of topical decongestant at baseline and after completion of the four week intervention. The findings from the endoscopic examination will be collected for research purposes and will be recorded using the grading system proposed by Lund and Kennedy.(Lund and Kennedy 1997)

**Endoscopic Findings**

| | None Present | Present |
|---|---|---|
| 1. Crusting | 0 | 1 |
| 2. Erythema | 0 | 1 |
| 3. Swelling | 0 | 1 |
| 4. Scar Band | 0 | 1 |
| 5. Purulent Drainage | 0 | 1 |
| 6. Thick Mucous | 0 | 1 |

| | None Present | Present in middle meatus | Present outside middle meatus |
|---|---|---|---|
| 7. Polyps | 0 | 1 | 2 |

**Radiologic Examination**

Radiologic examination, including CT scan of the sinuses, will not be required for enrollment in the study. Enrolled subjects who receive a CT scan of the sinuses for clinical reasons during the period of this study will have the results of the radiologic examination collected for research purposes and will be recorded according to the Lund MacKay system and possibly included in the data analysis. [40]

Radiological grading of the sinusal system proposed by Lund and Mackay.

| Sinusal system | Left | Right |
|---|---|---|
| Maxillary | | |
| Anterior ethmoid | | |
| Posterior ethmoid | | |
| Sphenoid | | |
| Frontal | | |
| Osteomeatal complex | | |
| Total score for each side | | |

Scores: Sinuses 0 = no alterations, 1 = partial opacification, 2 = total opacification
Osteomeatal complex: 0 = not occluded, 2 = obstructed

CT evidence of inflammation of the sinuses will be defined as mucosal thickening of at least one paranasal sinus and does not have to be severe enough to be classified as "partial opacification" or have a Lund and MacKay score of 1 or greater.

**Data Collection**

**Sources of Research Material** All research-related information, including responses to the selected patient-reported outcome measures, will be captured electronically via the use of dedicated iPADs. Week 2 patient-reported outcome measures will be captured via email link sent to subjects with RedCAP capture. All data will be stored in a specially designed database created by staff in the Clinical Outcomes Research Office using REDCap™ (Research Electronic Data Capture) software. Patient confidentiality will be maintained through the use of unique patient ID.

**Assessment of Treatment Efficacy** The change in the average SNOT-22 scores between baseline and four weeks will serve as the primary outcome measure in this study and will be calculated as:

Primary Outcome Measure, $\Delta$SNOT-22 = $\text{SNOT-22}_{\text{baseline}}$ — $\text{SNOT-22}_{\text{4-week follow-up}}$.

To assess the trajectory of change within subjects randomized to the two treatment arms the baseline, two-week, and four-week SNOT-22 assessment will be compared.

**Assessment of Treatment Safety -** Treatment safety will be assessed by patient interview and will include collection of adverse events experienced by the patient during the four week participation.

**Risk Assessment**

Budesonide has a potent glucocorticoid activity and weak mineralocorticoid activity. As an inhaled product, budesonide has an onset of action in 24 hours and peak effect in 1-2 weeks. The drug is well-tolerated and the more frequent side effects include: nose irritation, epistaxis, lightheadedness, and upset stomach.

At recommended daily doses in pediatric patients, no adverse effects were seen in the function of the hypothalamic-pituitary-adrenal (HPA) axis.(Brogden and McTavish 1992) In a study of 9 adult CRS patients who received budesonide in a manner similar as proposed in this study, no suppression of adrenal function was observed.(Sachanandani et al 2009)

**Data and Safety Monitoring**

The Clinical Outcomes Research Office (CORO) created a set of Standard Operating Procedures (SOPs) for the conduct of clinical research. These SOPS are developed, in part, from and are compliant with Institutional guidelines for the conduct of human research.

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations this study will have a monitoring board comprised of Drs. Piccirillo, Schneider, and Ms. Kukuljan knowledgeable about the risks of topically applied glucocorticosteroid, nasal anatomy, and Dr. Kallogjeri, the study biostatistician. All three individuals will not be part of the core study team. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event will be investigated by the monitoring team. All SAEs will be reported to Washington University HRPO.

**Statistical Analysis**

Comparison of within subject difference in SNOT22 scores between baseline and four-week follow-up between the 2 treatment groups will be the primary outcome measure. A clinically meaningful change is defined as a change of 9 or more on the SNOT22.

The change in SNOT22 is calculated as: $\Delta\text{SNOT-22} = \text{SNOT-22}_{\text{baseline}} - \text{SNOT-22}_{\text{4-week follow-up}}$

Independent samples t-test will be used to test for statistically significant difference in ΔSNOT-22 between 2 treatment groups.

The statistical significance of the observed difference in the percentage of subjects who achieve a clinically meaningful difference will be assessed with the chi-square statistic. The 95% confidence interval around the observed difference in the percentage of subjects who achieve a clinically meaningful difference will be calculated.

To assess the time trajectory of change within subjects randomized to the two treatment arms, the baseline, two-week, and four-week SNOT-22 assessments will be computed and compared. Within group differences will be compared using a repeated measure ANOVA. A general linear model (GLM) approach will be used to explore through the testing of an interaction effect (treatment group x time) whether the magnitude and pattern of change in SNOT-22 scores at baseline, 2 weeks, and 4 weeks is different between the 2 treatment groups. In addition to allowing for exploration of the interaction effect, the GLM model allows for evaluation of estimated means after controlling for potential confounders. A robust regression model will be used if the assumption of the GLM model will not be met.

The distribution of responses on the Clinical Global Impression (CGI) scale will be calculated within each intervention arm and the difference in responses between the two intervention arms will be compared for statistical significance with the chi-square statistic. All of the above analyses will be repeated within subgroups of nasal polyp and previous surgery subjects.

All statistical analyses will be performed with SAS software. Statistical significance will be defined as a two-tailed test of significance p value of 0.05 or less.

An interim analysis will be performed after Subject 32 has completed 4-week treatment. Stopping rules based on the work of O'Brien and Fleming [41] for the conduct of clinical trials will be followed.

An Intention-to-Treat analysis will be used for the final data analyses.

**Sample Size Calculations**

The sample size for this study was estimated using preliminary data from CRS patients undergoing steroid irrigations after sinus surgery. In addition our goal is to be able to detect a clinically meaningful difference of 0.8 points or greater in the change in SNOT-22 scores (pre-post) (equivalent to change of 9 or more points in the overall SNOT22 score) between the 2 treatment groups. Assuming that the variability (SD=1.1) in pre-post changes in SNOT-22 scores reported from Snidvong et al. will remain true in our data we estimated that we will need 32 subjects per group (total n=64) to be able to detect with 80% power at the 2 sided alpha level of 0.05 a difference of 0.8 points or greater in the in SNOT-22 score changes between the 2 treatment groups. We plan to enroll 80 subjects in total as we assume a 20% drop out/non-compliance rate.

**Remuneration**

Subjects will receive $45 after baseline and $45 at final visit and upon successful completion of trial.

**Timeline of the Study**

Subjects will be enrolled in the study for a total of four weeks. Given the volume of patients seen at the Adult Otolaryngology service with diagnosis of CRS, we anticipate it will take one year to complete enrollment.

| | Months | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Enrollment and Baseline assessment | | | | | | | | | | | | | | |
| Randomization | | | | | | | | | | | | | | |
| Treatment with Budosenide or Placebo | | | | | | | | | | | | | | |
| 2 weeks Assessment | | | | | | | | | | | | | | |
| 4 week assessment | | | | | | | | | | | | | | |
| Data analysis and Manuscript preparation | | | | | | | | | | | | | | |

**Calendar of Events (Patient)**

| Study Activity | Baseline (Time 0) | Week 1 | Week 2 | Week 3 | Week 4 |
|---|---|---|---|---|---|
| Consent | X | | | | |
| Randomization | X | | | | |
| SNOT-22 | X | | X | | X |
| ACE-27 Comorbidity | X | | | | |
| Physical examination | X | | | | X |
| Endoscopic examination* | X | | | | X |
| Radiological Examiniations (ex. CT sinus)* | X | X | X | X | X |
| Written instructions for administration of intervention | X | | | | |
| Intervention - budesonide or placebo | | X | X | X | X |
| Global Clinical Impression | | | | | X |
| Participant Stipend | X | | | | X |

* Includes tissue biopsy; Results only from nasal endoscopic examination and radiological examination performed for clinical purposes during the study will be collected for research purposes.

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