Study Protocol and Statistical Plan

Project Title: Efficacy of Mometasone Furoate Nasal Irrigation for Chronic Rhinosinusitis

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Abstract
Chronic rhinosinusitis (CRS),inflammation of the paranasal sinuses and lining of the nasal cavity for 12 weeks or more, affects up to the 12.5% of the US population and has a significant disease burden. Patients with CRS visit primary care physicians twice as often as those without the disease and have five times as many prescriptions filled. Based on national ambulatory data, rhinosinusitis accounts for more outpatient antibiotic prescriptions than any other diagnosis. The annual total direct and indirect cost of CRS exceeds $12 billion dollars.

Because of the chronic nature of the disease, medical therapy for CRS is focused on symptomatic management. Current first-line therapies include large-volume, low-pressure nasal saline irrigation, intranasal corticosteroids, and systemic antibiotics.
Nasal sinus saline irrigation is a widely recommended therapy for CRS. Several studies have demonstrated that large-volume, low-pressure nasal saline irrigation can improve distribution of pharmacologic therapeutics throughout the nasal cavity and sinuses, and enhance removal of mucus and bacteria/biofilms. As a result of the low-cost, excellent safety profile, and high patient compliance, nasal saline irrigation is an appealing long-term topical therapy for CRS.

While the efficacy and safety of intranasal corticosteroids (INCS), such as budesonide, are well-established for the long-term management of CRS, penetration of INCS into the paranasal sinuses is limited. A recent clinical trial led by Dr. Piccirillo and colleagues at Washington University demonstrated that the addition of budesonide capsules to daily large-volume, low-pressure sinus saline irrigation for one month resulted in clinically meaningful improvement in self-reported functional status and quality of life measures as well as objective measurements of CRS. Like budesonide, mometasone furoate (MF) is a second-generation INC. Mometasone is currently used as an inhalational drug for the treatment of asthma, allergic rhinitis, and nasal polyps. Due to its increased lipophilicity and extensive hepatic metabolism, however, mometasone has a markedly reduced systemic availability as compared to budesonide. In a recent double-blinded, placebo-controlled randomized clinical trial (RCT), Harvey et al demonstrated that MF nasal irrigation was superior to MF nasal spray in the management of CRS symptoms following sinus surgery, as measured by patient-reported outcomes and endoscopic findings.

The goal of this research project is to explore the impact of the addition of mometasone to high-volume, low-pressure nasal sinus saline irrigation (aka “Neti-Pot”-type systems) for surgery-naïve patients with CRS without nasal polyps. The overall objective of this study is to optimize medical management of CRS symptoms prior to escalation of surgery, and to evaluate a clinically meaningful question of whether steroid nasal irrigation is superior to steroid spray with saline nasal irrigation alone.

The specific aims of this study are as follows:
1. Compare the effectiveness of MF nasal irrigation to that of MF nasal spray in the management of CRS symptoms in surgery-naïve patients.
2. Evaluate the effect of MF nasal saline irrigation on the HPA axis compared to that of MF nasal spray.

To answer the research questions, the study design will be a double-blinded, randomized clinical trial. Up to 50 adult patients with complaints of purulent 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 8 weeks of either 1) mometasone nasal saline irrigation *and* placebo nasal spray or 2) mometasone nasal spray *and* nasal saline irrigation. The primary outcome measure will be the average per-patient change in *SNOT-22* between the two treatment groups.

SYNOPSIS

Study Title	Effectiveness of Mometasone nasal irrigation for chronic rhinosinusitis.
Objective	The primary objective of this proposed project is to evaluate the effectiveness of MF nasal saline irrigation as compared to the commonly used MF nasal spray in the medical management of CRS symptoms in patients who have not undergone sinus surgery.
Study Period	Planned enrollment duration for each subject: 8 weeks Planned study duration: I year
Number of Patients	Up to 50 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	Mometasone in the form of a nasal irrigation or nasal spray. Mometasone is an anti-inflammatory glucocorticoid steroid that is used for the treatment of asthma, allergic rhinitis, and nasal polyps
Study Design	Prospective randomized clinical trial
Inclusion and Exclusion Criteria	*Inclusion Criteria:* Adults 18-70 years of age 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, radiographic imaging showing inflammation of the paranasal sinuses *Exclusion criteria:* Unable to speak English Polyps in nasal cavity or the middle meatus History of comorbid ciliary dyskinesia, cystic fibrosis or any other mucociliary condition Dependence on prolonged corticosteroid therapy for comorbid conditions, such as asthma and chronic obstructive pulmonary disease. History of oral or systematic antibiotic use in the past 2 weeks History of sinus surgery History of cerebrospinal fluid leak History of allergy to mometasone 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 Known history of bleeding disorder, topical or injectable lidocaine allergy, use of blood thinners
Primary Outcome	The change in the SNOT-22 (©2006, Washington University, St. Louis, MO) score between baseline and eight-week intervention and calculated as: ΔSNOT-22 = $\text{SNOT-22}_{\text{baseline}}$ — $\text{SNOT-22}_{\text{8-week follow-up}}$.
Measurements	SNOT-22; ACE-27 Comorbidity Index; Lund Kennedy Endoscopy Grading Scale Lund – MacKay CT score (not required); Global Clinical Impression Scale;

	Olfactory Dysfunction Outcomes Rating (ODOR)
Statistical Methodology	Within subject change in SNOT-22 between intervention groups.

I. Statement of the Research Problem

Definition and Burden of Rhinosinusitis

Chronic rhinosinusitis (CRS) is the inflammation of the paranasal sinuses and lining of the nasal cavity for 12 weeks or more and is characterized by symptoms of facial pain-pressure-fullness, nasal discharge, and nasal obstruction.[1] 1 in 8 adults are affected and over 30 million cases are diagnosed each year.[2,3] Analysis of national ambulatory data demonstrates that rhinosinusitis accounts for more outpatient antibiotic prescriptions than any other diagnosis.[4] Patients with CRS visit primary care clinicians twice as often as those without the disorder and have 5 times as many prescriptions filled.[5] Approximately $8.3 billion is spent annually on CRS, primarily on prescription drugs and office-based care.[6] Surgery for CRS, which costs on average $7,700 per patient, is performed nearly 250,000 times per year in the United States.[7]

CRS is primarily an inflammatory disease, with exacerbations often associated with concomitant infection. However, 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.[1]

Medical Management

The medical management of CRS includes antibiotics, topical nasal steroid sprays, and 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.[8-20]

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, andthere have been over 12 studies examining the impact of saline irrigation in the management of CRS. A recent systematic review by Thomas et al. [17] analyzed the best mechanism to distribute topical therapeutics to the sinuses in CRS patients. Large-volume, low-pressure irrigation devices resulted in better distribution to the nasal cavity and sinuses, especially after surgery, than low-volume devices. In addition, large-volume devices were found to overcome any adverse effects of head position or nasal cavity anatomy on sinus distribution. Due to its low cost, high patient acceptance, and high benefit-to-risk margin, large-volume, low-pressure saline sinus irrigation is a widely recommended treatment for CRS. [7,11,14,15,17]

Topical Nasal Steroid Spray

Intranasal corticosteroid sprays (INCS) are established as safe and effective monotherapy or adjuvant treatments for CRS. [21,22] A Cochrane Review in 2011[22] examined the efficacy of topical steroids for CRS without polyps in five clinical trials. When compared to placebo, topical steroid improved symptom scores (standardised mean difference -0.37; 95% 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). While the use of INCS is generally recommended in the setting of CRS, there is limited penetration of the steroid beyond the nasal cavity and into

the paranasal sinuses. [23,24] Therefore, there has been great interest in the use of novel delivery approaches and devices to improve intra-sinus corticosteroid deposition.[25]

Non-Standard Delivery of Topical Steroids

Three studies have examined the use of topical steroids delivered through low-pressure, high-volume saline irrigation. Snidvongs et al.[22] examined a large cohort of patients with CRS (n=111), 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 outcomes were reported. An open-label prospective study (n=9) by Dr. Piccirillo and colleagues at Washington University[26] evaluated the efficacy of once daily irrigation with budesonide (0.25 mg). Subjects also underwent adrenal function assessment with the cosyntropin test before and after budesonide therapy. All subjects showed appropriate 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 significant. Steinke[27] conducted a prospective pilot study in 8 subjects with allergy, as defined by a positive skin prick test; 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. 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. Furthermore, in a recently completed double-blinded, placebo-controlled, randomized clinical trial by Piccirillo et al at Washington University (submitted), the addition of 1 mg of budesonide to daily large-volume, low-pressure sinus saline irrigation for one month resulted in clinically meaningful improvements in self-reported functional status and quality of life measures as well as objective measurements of chronic rhinosinusitis. Although the study included both patients with and without nasal polyps, patients with nasal polyps received only a minor benefit from budesonide. Patients with nasal polyps may have reduced topical application and penetration of budesonide as well as endotypes that are less responsive to the anti-inflammatory effects of glucocorticosteroids.

Like budesonide, mometasone furoate is a second-generation INC. The newest of the INCS, mometasone is currently used as an inhalational drug for the treatment of asthma, allergic rhinitis, and nasal polyps. Due to its increased lipophilicity and extensive hepatic metabolism, however, mometasone has a markedly reduced systemic availability as compared to budesonide (<0.1% versus 34%, respectively).[28] Furthermore, using various pharmacologic tests, including competition and McKenzie assays, mometasone has been shown to have higher potency than budesonide.[28] While corticosteroids can suppress the HPA axis, multiple studies have demonstrated that INCS have no significant impact on the HPA axis. In 6 randomized controlled parallel-group or placebo trials in adults and children, no evidence of HPA axis suppression was seen. [29]

In a recent double-blinded, placebo-controlled randomized clinical trial (RCT), Harvey et al demonstrated that MF nasal irrigation was superior to MF nasal spray in the management of CRS symptoms following sinus surgery, as measured by patient-reported outcomes and

endoscopic findings.[23] In the study, participants were assigned to either mometasone capsules (2 mg daily) or placebo intervention for 12 months following sinus surgery. The MF nasal irrigation group had a significantly greater improvement in nasal blockage visual analog symptoms compared to that of the MF nasal spray group (p=0.029). Furthermore, on endoscopic examination, the MF nasal irrigation group had significantly greater disease suppression than the MF nasal spray group, as evidenced by lower modified Lund-Kennedy endoscopic scores (p=0.018). Harvey et al reported no adverse effects from their dosage of mometasone.

Due to mometasone's favorable pharmacologic properties, we propose to evaluate the effectiveness of the addition of mometasone to large-volume, low-pressure sinus saline irrigation for patients with CRS without polyps in a single-site randomized clinical trial. We hypothesize that the addition of MF to a large-volume, low-pressure sinus saline irrigation will result in clinically meaningful benefits for patients with CRS as measured by subjective and objective outcome measures. We anticipate that MF dispensed in a large volume, low-pressure device will be superior to that of MF nasal spray combined with nasal saline irrigation in the medical management of CRS in surgery-naïve, non-polyp patients.

II. Specific Aims

The primary objective of this proposed project is to evaluate the effectiveness of MF nasal saline irrigation as compared to the commonly used MF nasal spray in the medical management of CRS symptoms in patients who have not undergone sinus surgery.
Specifically, we propose:

1. Compare the effectiveness of MF nasal irrigation to that of MF nasal spray in the management of CRS symptoms in surgery-naïve, non-polyp patients.

Participants will be randomized to either 1) 8-weeks of MF nasal saline irrigation *and* placebo nasal spray or 2) MF nasal spray *and* nasal saline irrigation. The primary outcome measure will be the within subject changes in SNOT-22 scores pre-and post-treatment. We hypothesize that MF nasal saline irrigation, when compared to that of MF nasal spray alone, will be more effective in the treatment of CRS symptoms.
2. Evaluate the effect of MF nasal saline irrigation on the HPA axis compared to MF nasal spray10 participants will be sampled from each study arm in order to ascertain the effect of mometasone nasal irrigation on the function of the hypothalamus-adrenal-pituitary (HPA) axis, as measured by the cosyntropin test before and after completion of intervention. In prior studies on the safety of MF nasal spray in children and adults, no discernible effects of MF nasal spray on the function of the HPA axis were reported.[29] To our knowledge, a study examining the impact of MF nasal saline irrigation on the HPA axis has not been performed. Based on prior studies demonstrating the safety of MF nasal spray, we hypothesize that MF nasal saline irrigation will have a negligible effect on the HPA axis. Furthermore, subjects will be queried throughout their participation in the study regarding any adverse events experienced with mometasone.

III. Experimental Plan, Methods, and Data Analysis

Study Design: Randomized clinical trial
Subjects: Up to 50 adult patients with complaints of purulent 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:
Adults 18-70 years of age
Twelve (12) weeks or longer of two or more of the following signs and symptom consistent with chronic rhinosinusitis (CRS)[30,31].
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, and/or
radiographic imaging showing inflammation of the paranasal sinuses

Exclusion criteria:
Unable to speak English
Current nasal polyps
Previous sinus surgery
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 cerebrospinal fluid leak
History of allergy to mometasone 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 are 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[32]. Presence of rhinosinusitis-specific comorbidities will include: inhalant allergies, asthma, and aspirin sensitivity.

Randomization

Using a randomization scheme with permuted blocks of varying sizes, participants will be randomized to receive 8 weeks of either 1) MF nasal saline irrigation (2.4 mg) *and* placebo nasal spray or 2) MF nasal spray (50 mcg/spray) *and* nasal saline irrigation.

Intervention

MF nasal spray is currently dosed at 2 sprays/nostril for a total amount delivered of 200 mcg. When a patient administers a nasal spray, approximately 70% of the dose is cleared from the nose into the throat and swallowed. The remaining 30% remains deposited in the nose. Therefore, if a patient receives 200 mcg of mometasone nasal spray, only 60 mcg of this dose remains in the nasal cavity. [28] Personal communication with Advanced Rx and review of the literature regarding fluid/topical nasal residuals suggests that a total of 2.4 mg of MF powder reconstituted in 240 mL of nasal saline is an equivalent dose to that of the metered spray.

Calculations
Steroid nasal spray
200 mcg dose of steroid nasal spray, 30% of the dose is retained in the nasal cavity

200 mcg x 0.30= 60 mcg in the nasal cavity

Steroid Nasal Irrigation
Mometasone 2.4 mg dissolved in 240 mL of saline
2.5% of the dose remains in the nasal cavity following irrigation
2.4 mg x 0.025= 0.06 mg or 60 mcg

Harvey et al recently completed a study evaluated the effectiveness of mometasone nasal irrigation dosed at 2 mg daily for management of CRS symptoms following sinus surgery with no adverse effects reported during the study's yearlong duration.[30]

Participants will be provided with a 2-month supply of either 1) MF nasal spray *and* nasal saline irrigation *or* 2) MF nasal irrigation *and* placebo nasal spray.

All participants will be provided with an 8-ounce (240 ml) NeilMed Sinus Rinse Regular Bottle Kit and a two-month supply of USP Grade Sodium Chloride & Sodium Bicarbonate Mixture (pH balanced, Isotonic & Preservative & Iodine Free) commercially prepared packets. 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 (either mometasone or lactose placebo) 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.

For participants randomized to MF nasal spray, they will be instructed to perform the following once daily: nasal saline irrigation with lactose placebo capsules as outlined above immediately followed by 2 sprays per nostril of MF nasal spray. For participants receiving MF nasal irrigation, they will be instructed to perform the following once daily: nasal saline irrigation with mometasone capsules as outlined above immediately followed by 2 sprays per nostril of the placebo spray.

Each study bottle (Mometasone capsule, placebo capsule, mometasone nasal spray, placebo nasal spray) will be assigned with a number from 1-50. Only Dr. Kallogjeri will have a list that links the treatment type (Mometasone nasal irrigation arm versus mometasone nasal spray arm) with the bottle number. The subject and the rest of the study team will remain blinded to the randomization assignment. 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 Jiramongkolchai and information will be shared with the medical staff assuming care for the patient.

The mometasone capsules and mometasone spray will be prepared by Advanced Rx Pharmacy, Plymouth Meeting, Pennsylvania.

Advanced Rx will provide the mometasone capsules and placebo capsules free of charge. The cost of a 30 day supply of mometasone nasal spray will be $79/study participant. Likewise, the cost of a 30 day supply of placebo nasal spray will be $79/study participant. Therefore, the cost for the active mometasone spray + placebo nasal irrigation will be $158/study participant and the cost for the placebo nasal spray + mometasone nasal irrigation will be $158/study participant.

A randomized list will be provided to Advanced Rx and the medications mailed directly by Advanced Rx to the study participants.

Mometasone Nasal Irrigation
Mometasone is an anti-inflammatory glucocorticoid steroid that is used for a variety of common ailments. Among conditions related to the respiratory tract, mometasone is used as an inhalational drug for the treatment of asthma, allergic rhinitis, and nasal polyps. The mechanism of action of mometasone 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.[28]

Subjects randomized to the mometasone nasal irrigation intervention arm will be required to mix 2.4 mg of mometasone 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 mometasone 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.

Placebo Nasal Spray

The placebo nasal spray will be packaged in the same bottle as that of MF nasal spray. The nasal spray will prepared by Advanced Rx Pharmacy and will contain the same inert ingredients found in MF nasal spray: glycerin, microcystralline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80. Subjects in the mometasone nasal irrigation arm will be instructed to first irrigate with mometasone followed by use of the placebo nasal spray.

Mometasone Nasal Spray

Subjects randomized to the mometasone spray intervention arm will receive a 2 month supply of MF nasal spray (50 mcg/spray), which is commercially available as Nasonex™, but will be prepared for the study by Advanced Rx Pharmacy. Participants will be instructed to use 2 sprays per nostril once a day followed by nasal saline irrigation

Placebo Nasal Irrigation

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

Cosyntropin Test

Measuring blood levels of cortisol after cosyntropin stimulation is the gold standard to evaluate effects of exogenous corticosteroids on the HPA axis. The effects of mometasone nasal spray on the hypothalamus-pithuitary-adrenal (HPA) axis have been evaluated in 6 clinical trials in both adults and children (dose range 100 ug once daily to 400 ug twice daily). In all 6 trials, no effects of mometasone nasal spray on the HPA axis was discernible.[29] To our knowledge, a similar demonstration of the safety of a nasally administered mometasone wash has not been performed. As a result, ten participants from each study arm will be selected for an optional cosyntropin test to assess the effect of mometasone nasal irrigation on the HPA axis.

Baseline levels of serum cortisol will be measured at the subject's first visit. Subjects will then receive 0.25 mg of cosyntropin and 10 mg of mannitol reconstituted with 1 mL of 0.9% sodium chloride as an intramuscular injection to stimulate the adrenal cortex. Serum will be drawn 30 minutes and cortisol level measured. This test will be repeated upon the completion of 60 days of mometasone nasal irrigation or spray. If mometasone is absorbed systematically via nasal irrigation, serum cortisol should be inappropriately low upon cosyntropin stimulation compared to baseline. No change in serum cortisol is expected in the mometasone nasal spray group based on prior studies. The cosyntropin test will be performed at the Center for Outpatient Health and blood cortisol levels measured by the General Clinical Research Center Immunoassay Core Laboratory.

In the event that at the first pre-intervention cosyntropin visit, a post-stimulation level is below the critical level of 18 µg/dL, indicating an insufficient adrenal response, the PI will be notified and the study participant contacted. With an abnormal cortisol level pre-intervention, the study participant will not be eligible for further participation in the study and the study coordinator will recommend that the participant be evaluated by his/her primary care physician.

In the event that a post-stimulation level is below the critical level of 18 µg/dL indicating an insufficient adrenal response, the PI will be notified and the study coordinator will notify the patient and recommend a referral to the study participant's primary care physician. Study participants in either intervention arm will remain on the intervention until cosyntropin lab values are received and reviewed.

Because certain medical conditions and medications can affect the cosyntropin test and result in spurious results, subjects will also be excluded from the test if they met any one of the following criteria: concurrent or recent use (within the past 30 days) of systemic corticosteroids; history of pituitary disease; morbid obesity as measured by body mass index; concurrent or recent use of medications that accelerate the clearance of cortisol, such as dilantin, rifampin, amphetamines, or lithium carbonate; concurrent use of medications that interfere with the production of cortisol, such as ketoconazole, amphotericin B, bupropion, Echinacea, fluoroquinolones, itraconazole, licorice, and ma huang (Ephedra); use of oral contraception; use of female or male hormone therapy; a radioactive scan performed within 7 days before the test; known hypersensitivity to cortisol, corticotropin, or cosyntropin; allergic disease associated with anaphylactic reactions or breathing difficulties; or pregnancy.

Exemption From IND Requirements
The use of mometasone 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 mometasone in this study fulfills all of the criteria for exemption:

1. Mometasone 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 mometasone.
5. The study will be conducted in compliance with the requirements for review by an IRB (21 CF R part 56) and with the requirements for informed consent (21 CFR part 50).
6. The study is not intended to promote or commercialize mometasone.

Concomitant Medications
At the time of enrollment, subjects may already be using a topical nasal steroid medication (ie., fluticasone or Flonase®) or nasal irrigation. Participants who have been previously using a nasal spray or nasal irrigation will be asked to discontinue use while enrolled in the study.

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.[33] 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 9 points.[33,34]

Primary Outcome Measure
Study participants will be asked to complete the SNOT-22 at baseline, two weeks, four weeks, six weeks, and eight weeks following start of medications. The SNOT-22 score will be calculated as the average per item score for each of the 22 items and the value will range between 0 and 5. For subjects who answer less than 22 items (i.e., don't completely answer the SNOT-22), the total score will be the average per item value for the items that were answered. The change in SNOT-22 scores between baseline and eight weeks will serve as the primary outcome measure in this study and will be calculated as:

Primary Outcome Measure, ΔSNOT-22 = $\text{SNOT-22}_{\text{baseline}}$ — $\text{SNOT-22}_{\text{8-week follow-up}}$.

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

Secondary Outcome Measure.

University of Pennsylvania Smell Identification Test (UPSIT):
The UPSIT is a test of olfactory identification and consists of four 10-page booklets, with a total of 40 items. On each page, there is a different “scratch and sniff” strip and four choice options. Subjects are asked to scratch each strip with a pencil to release the scents, detect the smell, and identify the smell from the four choice options. The UPSIT comes from a scoring rubric that identifies the normalcy benchmark based on age and gender. The UPSIT is commercially available, takes 10-15 minutes to complete, and is the gold standard test to assess smell identification. Subjects will complete the UPSIT at their baseline and final visit.

Clinical Global Impression Scale (CGI):
The overall response to treatment will be measured with a modification of the Clinical Global Impression (CGI) scale. [32,35] 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*.
In addition, subjects will be asked to rate their subjective sense of smell pre- and post-intervention.

Questionnaire for Olfactory Dysfunction (QOD):
The QOD is a validated quality of life questionnaire for patients with olfactory disorders. Subjects will complete the QOD at their baseline and final visit.

Olfactory Dysfunction Outcomes Rating (ODOR):
The ODOR is a quality of life measure capturing physical, functional, and emotional limitations specific to smell loss. It is currently undergoing validation and is designed to be more concise, readable, and comprehensive than the QOD. Subjects will complete the ODOR questionnaire at their baseline and final visit.

Physical Examination including nasal endoscopy performed for clinical purposes The physical examinations will be done as part of routine care during the patients’ scheduled clinic visit. 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.[36]

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.[36,37]

Sinus system	Left	Right
Maxillary		
Anterior ethmoid		
Posterior ethmoid		
Sphenoid		
Frontal		
Ostiomeatal complex		

*Scores
Sinuses: 0= no mucosal thickening, 1= partial opacification, 2= total opacificiation
OMC: 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.. Week 2, Week 4, and Week 6 patient-reported outcome measures will be captured via an email sent to subjects with direct linkage to REDCap™ (Research Electronic Data Capture). All data will be stored in a specially designed database created by staff in the Clinical Outcomes Research Office using REDCap™. 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 eight weeks will serve as the primary outcome measure in this study and will be calculated as:

Primary Outcome Measure, ΔSNOT-22 = SNOT-22$_{\text{baseline}}$ — SNOT-22$_{\text{8-week follow up}}$.

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

Assessment of Treatment Safety: As described above, 10 participants from each study arm will be selected for a cosyntropin test to assess for effects of mometasone nasal irrigation on the HPA axis. Treatment safety will also be assessed by patient interview and will include collection of adverse events experienced by the patient during the eight-week participation.

Risk Assessment: Mometasone has a potent glucocorticoid activity and weak mineralocorticoid activity. As an inhaled product, mometasone has an onset of action in 24 hours and peak effect between 1-4 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 both pediatric and adult patients, no adverse effects were seen on the HPA axis. [29]

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 Dr. Piccirillo and Ms.

Kukuljan knowledgeable about the risks of topically applied glucocorticosteroid, nasal anatomy, and Dr. Kallogjeri, the study biostatistician. The monitoring board will meet to review data at least every 6 months. 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 eight-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 points on the SNOT22 (scored as the average per item value for each of the 22 items). The change in SNOT22 is calculated as: ΔSNOT-22 = SNOT-22$_{\text{baseline}}$ — SNOT-22$_{\text{8-week follow-up}}$. 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, 2 week, 4 week, 6 week, and 8 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, 4 weeks, 6 weeks, and 8 weeks are 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 statistical analyses will be performed with the appropriate statistical software e.g. SAS, SPSS. Statistical significance will be defined as a two-tailed test of significance p value of 0.05 or less.
Stopping rules based on the work of O'Brien and Fleming [38] 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 calculated based on achieving a difference of 9 points or more on *SNOT-22* scores. Thus, to be able to detect with 80% power at the 2-sided alpha level of 0.05 a difference of 9 points or greater between the 2 treatment groups, a total of 50 subjects- 25 subjects per group- will be necessary. With an anticipated 15% drop out/non-compliance rate, the total sample size planned for this study will be 44 subjects.
Remuneration: Subjects will receive $50 after baseline and $50 at final visit and upon successful completion of trial.
For subjects who complete the coynstropin test, they will receive up to an additional $100. Subjects will receive $50 after the baseline cosyntropin test and another $50 following the second cosyntropin test.

Timeline of the Study

Subjects will be enrolled in the study for a total of eight 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.

Calendar of Events (Patient)

Study Activity	Baseline (Time 0)	Week 1	Weeks 2,4,6	Week 8
Consent	X			
Randomization	X			
SNOT-22	X		X	X
Cosyntropin test with blood draw	X			X
ACE-27 Comorbidity	X			
ENT Physical examination w/ Endoscopic examination*	X			X
Radiological Examinations (ex. CT sinus)*	X	X	X	X
Written instructions for administration of intervention	X			
Intervention - mometasone nasal irrigation or mometasone nasal spray		X	X	X
Global Clinical Impression	X	X	X	X
Questionnaire for Olfactory Dysfunction	X			X
Olfactory Dysfunction Outcomes Rating (ODOR)	X			X
UPSIT	X			X
Participant Stipend	X			X

* 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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