THE University of Vermont MEDICAL CENTER

Research Protocol

An open-label, prospective, randomized, pilot clinical study to study the effectiveness of MEDIHONEY® rinses (alone or in combination with intranasal corticosteroids) compared to intranasal corticosteroid rinses in patients with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) following Functional Endoscopic Sinus Surgery (FESS).

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Protocol Summary:

Chronic rhinosinusitis is a disease characterized by inflammation of the mucosa of the nose and paranasal sinuses that can present with or without nasal polyposis. Nasal polyposis is a pathologic condition associated with chronic inflammation and eosinophilia of the nasal mucosa, thought to be triggered by allergy, infection or other environmental irritants. Although multiple theories exist regarding the formation of nasal polyps, the true cause of the disease is unknown. Thus, while multiple medical and surgical therapies exist, this disease can often be challenging to treat because effective, long-term treatments are suboptimal.

The mainstay of treatment includes antibiotics and topical and systemic steroids, with surgery reserved for patients refractory to medical management. After successful functional endoscopic sinus surgery (FESS), medical management is still required in the long-term. Even with appropriate post-operative management, recurrence rates have been reported as high as 60%, often necessitating revision surgery. It is clear that a better understanding of chronic rhinosinusitis with nasal polyposis is needed to achieve better clinical outcomes and develop new therapies that are safe, effective and inexpensive.

This study is a prospective, randomized, pilot clinical study that will be carried out with adult patients from the Otolaryngology Division at The University of Vermont Medical Center with a diagnosis of refractory CRSwNP, and who have elected surgery as a treatment method. It seeks to determine whether the use of MEDIHONEY® sinus rinses (alone or in combination with intranasal steroids) in the postoperative period enhances recovery and prevents polyp recurrence in patients after functional endoscopic sinus surgery (FESS), compared with the standard regimen of intranasal corticosteroid sinus rinses. The study will collect and compare subjective and objective efficacy assessments of both types of rinses.

In patients with refractory CRSwNP, FESS is intended to restore physiologic sinus ventilation and drainage, which can facilitate the gradual resolution of mucosal disease. However, because FESS does

not directly treat the underlying inflammatory disorder, sinus surgery must be followed by medical management to control inflammatory processes or symptoms will invariably return. The mainstay of maintenance treatment is a short-term oral corticosteroid regimen with frequent normal saline nasal rinses, followed by a return to corticosteroid and normal saline irrigation. At times, antibiotics can be added as well since CRSwNP is a disorder whose pathophysiology involves bacterial infection often with resistant strains. Currently our patients at The University of Vermont Medical Center receive a moderate oral corticosteroid taper regimen for the first 7 days following FESS, followed by up to 6 months of intranasal corticosteroid in normal saline rinses.

The intranasal steroids have their limited but documented side effects and antibiotics can induce resistance. A semi-natural product like MEDIHONEY®, with antibacterial and anti-inflammatory properties, might prove as a useful alternative since it has no major adverse events documented in the literature, does not induce resistance and is effective against resistant pathogens common in this patient population. Honey has been used as a natural remedy for centuries. More recently, honey has been proven to have antibacterial and antibiotic properties and has become a part of the modern armamentarium of therapies for chronic wounds. Based on current knowledge about the nature of CRSwNP, honey might be a natural, inexpensive and safe alternative or addition to current therapies. If proven to be effective it could play a valuable role in the treatment of chronic rhinosinusitis with nasal polyposis.

In this study, we will evaluate the effect of MEDIHONEY® rinses (alone or in combination with intranasal corticosteroids) compared to intranasal corticosteroid rinses in Patients with Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) following Functional Endoscopic Sinus Surgery (FESS).

This study will involve CRSwNP patients bound for surgery. Patients will be seen as per the usual regimen at The University of Vermont Medical Center on the initial visit (when FESS is discussed), the day of the surgery, and follow-up at days 7, 35, 91, 119 and 182 (6th month). The outcome measurements in this study are based on the recommendations of The Rhinosinusitis Initiative (2006) which was developed by 5 national societies, of the Task Force on Rhinosinusitis of the American Academy of Otolaryngology-Head and Neck Surgery (1997) and of The Staging and Therapy Group (1995). These recommendations provide templates for clinical trials in therapies for CRSwNP and also appendices for validated tools in assessing the outcome measures.

Patients' demographic data and their relevant past medical history (form 1) will be collected from the patient at baseline. . They will undergo a routine complete physical examination as done routinely (form 3). Additionally, the physical exam will entail checking for anatomic variations at baseline (Form 1.5), and an assessment of symptoms reflective of toxicities using a modified version of the Common toxicity Criteria (CTC) at all visits (form 4). A routine endoscopy scoring will be carried out using the validated Lund-Kennedy scoring scale to stage the disease at all visits [14, 15]. Patients will be asked to answer questions to one additional survey that is not usually done in practice to assess nasal symptoms at baseline and on follow-ups and to determine their quality of life (QOL) (form 7). These are documented confounding variable in the literature. On the day of surgery, a surgical staging of the patients' disease will be undertaken (form 8), along with an intraoperative collection of nasal drainage to be sent for culture. A similar culture will be done on day 35.

Purpose and Objectives:

Chronic rhinosinusitis (CRS) is a disease characterized by inflammation of the mucosa of the nose and paranasal sinuses that can present with (CRSwNP) or without nasal polyposis. Nasal polyposis is a pathologic condition associated with chronic inflammation and eosinophilia of the nasal mucosa, thought to be triggered by allergy, infection or other environmental irritants. Although multiple theories exist regarding the formation of nasal polyps, the true cause of the disease is unknown. Thus, while multiple medical and surgical therapies exist, this disease can often be challenging to treat because effective,

long-term treatments are suboptimal [1].

With an increasing prevalence, CRS affects nearly 15% of the US population and is one of the most expensive chronic disorders experienced by the North American population [1].

The mainstay of treatment of CRSwNP includes antibiotics and topical and systemic steroids. In patients with refractory CRSwNP, functional endoscopic sinus surgery, known by the acronym FESS, is intended to restore physiologic sinus ventilation and drainage, which can facilitate the gradual resolution of mucosal disease. However, because FESS does not directly treat the underlying inflammatory disorder, a successful sinus surgery must be followed by medical maintenance therapy to control inflammatory processes [2]. Left alone, polyps usually reaccumulate within a few years without medical maintenance therapy [2, 3]. Even with appropriate post-operative management, recurrence rates have been reported as high as 60%, often necessitating revision surgery. It is clear that a better understanding of chronic rhinosinusitis with nasal polyposis is needed to achieve better clinical outcomes and develop new therapies that are safe, effective and inexpensive.

The mainstay of maintenance treatment is glucocorticoid nasal spray [4, 5] and saline irrigation [6] in all patients for 12 weeks. Oral antibiotics can also be given for a 2 week period postoperatively [3, 7]. An oral steroid course is an accepted regimen following FESS in current practice [8]. It can be introduced in the perioperative period (varying from the day of surgery to the 2 weeks preceding surgery [9, 10]) and is then stopped in the first week [11] or 2 weeks [12] following FESS. There is evidence that administration of systemic steroids in the postoperative period for patients who have polyps may have a significant impact on their postoperative course [11]. The chance of significant side effects increases with the dose and duration of treatment and therefore the minimum dose necessary to control the disease should be given [13]. Thus, at The University of Vermont Medical Center, patients usually receive a moderate 40mg oral prednisone taper regimen for the first 7 days following the surgery. This regimen is believed to be sufficient for effective clinical activity and to mitigate the potential undesirable short-term side effects associated with higher doses.

Topical steroids have their limited but documented side effects and antibiotics can induce resistance. A semi-natural product like manuka honey (brand name MEDIHONEY®), with antibacterial and anti-inflammatory properties, might prove as a useful alternative since it has no major adverse events documented in the literature, does not induce resistance and is effective against resistant pathogens common in this patient population.

Honey has been used as a natural remedy since the ancient Greeks and Egyptians use of it in wound care [14]. More recently, manuka honey has been proven to have antibacterial and antibiotic properties and has become a part of the modern armamentarium of therapies for chronic wounds.

CRS is an inflammatory disease in which bacteria are commonly implicated often in the form of a biofilm [15]. Pseudomonas aeruginosa and Staphylococcus aureus are two pathogens that, along with their biofilms, are important in the pathophysiology of CRS [15, 16].

In vitro Manuka honey is an effective in vitro treatment against these pathogens both in the planktonic and in the biofilm forms at concentrations that are attainable in clinical use [16, 17]. MEDIHONEY® is also against resistant strains of bacteria which can be helpful in a small but significant number of cases of CRSwNP [18]. Methylglyoxal (MGO) is highly concentrated in manuka honey and is believed to be its major antibacterial compound, contributing the relatively superior antimicrobial activity of manuka honey compared to non-MGO honeys [19]. However, MGO is only partially responsible for the antibiofilm [19] and cidal (against resistant bacteria) [20] activities of manuka honey.

In a preclinical rabbit model, using concentrations that are cidal against bacterial biofilms in vitro, the application of a manuka honey solution to rabbit nasal respiratory mucosa over different treatment intervals (since it is currently unknown for how long a patient would need to be treated) is safe with no evidence of

histological epithelial injury [15].

In the clinical setting, a handful of prospective observational studies and case series/reports of different sizes show a positive association between the use of MEDIHONEY® and wound healing with outcome measures such as the resulting antibacterial activity, pain, size decrease, and wound odor in chronic wounds after treatment with honey. In these studies, MEDIHONEY® has been successfully used in different contexts of wound healing among chronically ill patient populations, including chronic pressure ulcers in spinal cord-injured patients [21], slowly healing wounds in critically ill neonates [22], wounds in pediatric oncology patients [23], wounds of various etiologies (post-operative, pressure ulcers, soft tissue infections, general wounds, burns/scalds and skin lesions) [24], and leg ulcerations in patients with recalcitrant disease [25, 26]. Case reports of two patients with allergic fungal rhinosinusitis (AFRS), a subtype of CRS that accounts for 7% of cases necessitating surgery [27, 28], who had undergone FESS but continued to develop sinus disease, and whose ineffective steroid irrigation treatment regimen was changed to add Manuka honey saline irrigations, show the patients' objective and subjective efficacy assessments improving drastically [29].

In randomized controlled trials, MEDIHONEY® has been shown to have effective wound healing properties compared to conventional wound dressings [30] and also to have an effective action against antibiotic-resistant microorganisms in patients with central venous catheters compared to an antibiotic [31]. Two randomized controlled studies exist looking at the role of honey in the context of rhinosinusitis. Thamboo et al. [32] studied the effect of MEDIHONEY® in patients with allergic fungal rhinosinusitis (AFRS), a subset of rhinosinusitis, who were resistant to conventional medical treatment after bilateral functional endoscopic sinus surgery (FESS) and maximal postoperative medical management. These patients were given the honey (50/50 mixture of honey-saline solution) in the treated nostril and only saline in the control nostril. By 30 days, objective efficacy assessment tools (endoscopic grading and ethmoid cavity fungal culture) did not demonstrate a global improvement, however patients' subjective assessment of their nasal symptoms showed significant symptomatic benefits. It is worth mentioning that a subset of patients with worse disease did show improvements in the objective assessment tools as well. In a double-blinded randomized controlled study by Chang et al. [33], patients with CRS undergoing bilateral FESS received a manuka honey-soaked middle meatal spacer in the treated nostril and a nonmedicated spacer in the control nostril. These spacers are nasal packings used for 7 days to minimize inflammation and formation of scar tissue following the surgery. Upon removal, biopsies of the mucosa showed no significant change in inflammation between the nostrils, though patients had less pain upon removal of these spacers. Based on current knowledge about the nature of CRSwNP, honey has been proposed as a potential treatment option but its utility has not been fully investigated. MEDIHONEY® has numerous advantages; it is natural, inexpensive and has been proven to be safe for use in respiratory mucosa. If proven to be effective it could play a valuable role in the treatment of CRSwNP, either as an alternative or an addition to the current maintenance regimen.

The aim of this study is to determine if the use of MEDIHONEY® rinses (alone or in combination with intranasal corticosteroids) is an effective means to enhancing recovery and preventing polyp recurrence in patients after FESS, compared with the standard regimen of topical corticosteroid sinus rinses.

Primary Study Objectives:

1) To assess the effect of MEDIHONEY® (alone or in combination with intranasal corticosteroids) vs. intranasal corticosteroid sinus rinses on mucosal healing and polyp recurrence in the post-operative period following FESS, using the objective Lund-Kennedy endoscopic scores.
   - *Hypothesis: MEDIHONEY® alone and MEDIHONEY® in combination with intranasal corticosteroids are both at least as effective or better than intranasal corticosteroid sinus rinses on mucosal healing and polyp recurrence in the post-operative period following FESS, using the objective Lund-Kennedy endoscopic scores.*

Secondary study objectives:

2) To assess the effect of MEDIHONEY® (alone or in combination with intranasal corticosteroids) vs. intranasal corticosteroid sinus rinses on patient quality of life in the post-operative period following FESS:

a. using the objective nasal drainage cultures;

- *Hypothesis: MEDIHONEY® alone and MEDIHONEY® in combination with intranasal corticosteroids are both at least as effective or better than intranasal corticosteroid sinus rinses on mucosal healing and polyp recurrence in the post-operative period following FESS, using the objective nasal drainage cultures' results.*

b. using the subjective SNOT 22 questionnaire to assess overall quality of life;

- *Hypothesis: MEDIHONEY® alone and MEDIHONEY® in combination with intranasal corticosteroids are both at least as effective or better than intranasal corticosteroid sinus rinses on mucosal healing and polyp recurrence in the post-operative period following FESS, using the subjective SNOT 22 questionnaire.*

c. using the subjective SNOT 22 questionnaire to assess nasal symptoms;

- *Hypothesis: MEDIHONEY® alone and MEDIHONEY® in combination with intranasal corticosteroids are both at least as effective or better than intranasal corticosteroid sinus rinses on mucosal healing and polyp recurrence in the post-operative period following FESS, using the subjective SNOT 22 questionnaire.*

Methods and Procedures:

This study is a prospective, randomized, pilot clinical trial that will be carried out with patients from the Otolaryngology Division at The University of Vermont Medical Center to determine if the use of MEDIHONEY® sinus rinses (alone or in combination with intranasal steroids) in the postoperative period enhances recovery and prevents polyp recurrence in patients after functional endoscopic sinus surgery (FESS), compared with the standard regimen of topical corticosteroid sinus rinses. The study will collect and compare subjective and objective efficacy assessments of both types of rinses.

In patients with refractory CRSwNP, functional endoscopic sinus surgery, known by the acronym FESS, is intended to restore physiologic sinus ventilation and drainage, which can facilitate the gradual resolution of mucosal disease. However, because FESS does not directly treat the underlying inflammatory disorder, sinus surgery must be followed by medical management to control inflammatory processes or symptoms will invariably return [2]. Left alone, polyps usually reaccumulate within a few years without medical maintenance therapy [2, 3]. The mainstay of maintenance treatment is glucocorticoid nasal spray [4, 5] and saline irrigation [6] in all patients for 12 weeks. Oral antibiotics can also be given for a 2 week period postoperatively [3, 7]. An oral steroid course is an accepted regimen following FESS in current practice [8]. It can be introduced in the perioperative period (varying from the day of surgery to the 2 weeks preceding surgery [9, 10]) and is then stopped in the first week [11] or 2 weeks [12] following FESS. There is evidence that administration of systemic steroids in the postoperative period for patients who have polyps may have a significant impact on their postoperative course [11]. The chance of significant side effects increases with the dose and duration of treatment and therefore the minimum dose necessary to control the disease should be given [13]. Thus, at The University of Vermont Medical Center, patients usually receive a moderate 40mg oral prednisone taper regimen for the first 7 days following the surgery. This regimen is believed to be sufficient for effective clinical activity and to mitigate the potential undesirable short-term side effects associated with higher doses.

Topical steroids have their limited but documented side effects and antibiotics can induce resistance. A semi- natural product like MEDIHONEY®, with antibacterial and anti-inflammatory properties, might

prove as a useful alternative since it has no major adverse events documented in the literature, does not induce resistance and is effective against resistant pathogens common in this patient population.

This study will involve CRSwNP patients bound for surgery. Patients will be seen as per the usual regimen at The University of Vermont Medical Center on the initial visit (when FESS is discussed or till day of preoperative computed tomography (CT) scan), the day of the surgery, and follow-up at days 7 (postop week 1), 35 (5), 91 (13), 119 (17) and 182 (26, also month 6). Baseline assessments can be combined with day of surgery when applicable. The outcome measurements in this study are based on the recommendations of The Rhinosinusitis Initiative (2006) which was developed by 5 national societies [34], of the Task Force on Rhinosinusitis of the American Academy of Otolaryngology-Head and Neck Surgery (1997) [35] and of The Staging and Therapy Group (1995) [36]. These recommendations provide templates for clinical trials in antimicrobial, anti-inflammatory, and symptom-relieving therapies for CRSwNP and also appendices for validated tools in assessing the outcome measures.

Patients' demographic data, their relevant past medical history and their preoperative imagery score will be collected from the patient at baseline (form 1). They will undergo a routine complete physical examination as done routinely (form 3). Additionally, the physical exam will entail checking for anatomic variations at baseline (form 1.5), and an assessment of symptoms reflective of toxicities using a modified version of the Common toxicity Criteria (CTC) at all visits (form 4). A routine endoscopy scoring will be carried out using the validated Lund-Kennedy scoring scale to stage the disease [35, 36]. Patients will be asked to answer to answer questions to one additional survey that is not usually done in practice to assess the baseline severity of their symptoms at baseline and on follow-ups and to determine their quality of life (QOL) (form 7). On the day of surgery, a surgical staging of the patients' disease will be undertaken (form 8), along with an intraoperative collection of nasal drainage to be sent for culture. A similar culture will be done on day 35.

The administration of all tests to measure these outcomes will occur during the patients' regular visits to clinic as per current practice, necessitating more time. It will not result in any delays in treatment.

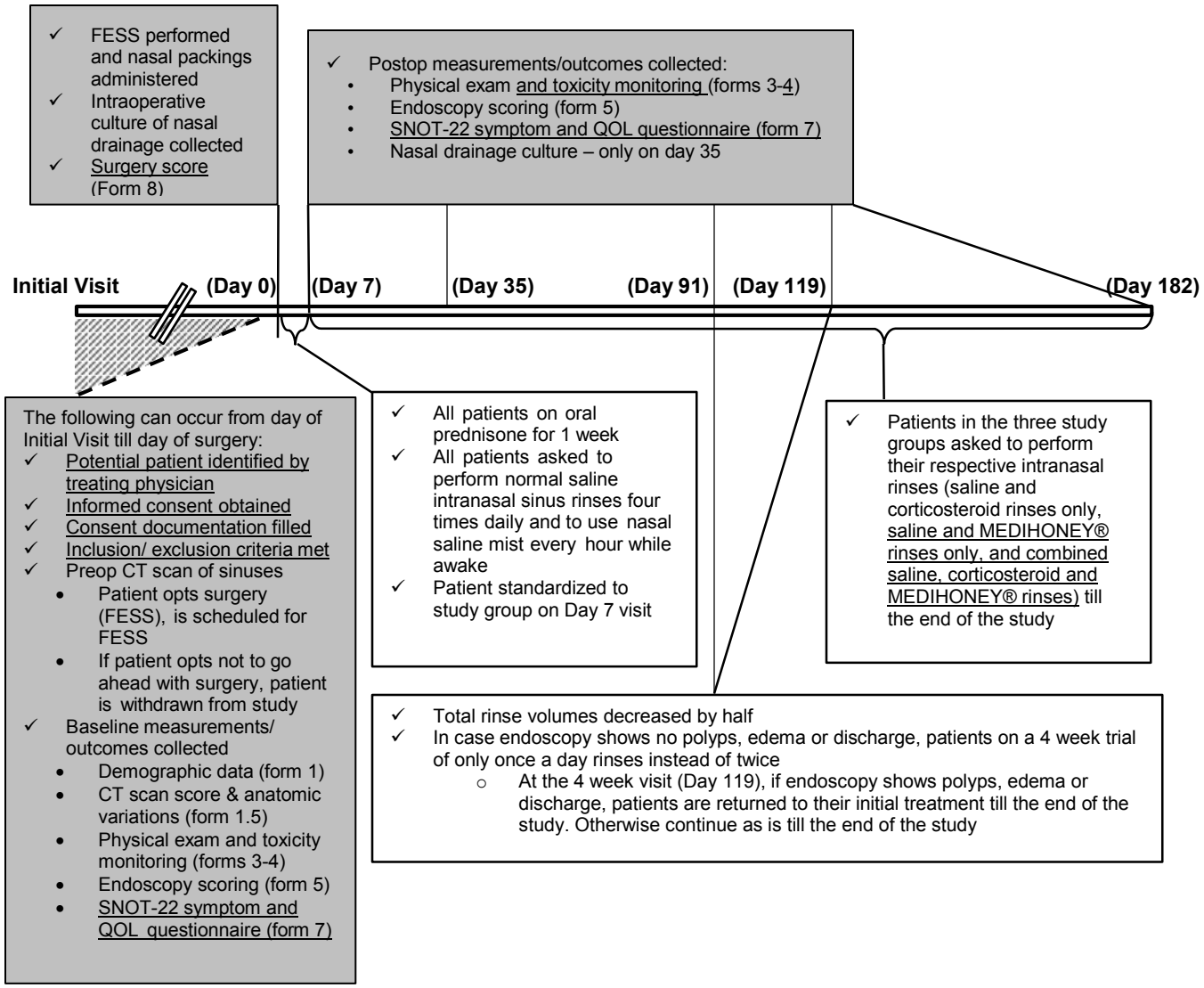
Inclusion criteria for patient enrollment into this study will include:

1. Age 18 years or older;
2. Diagnosis of CRSwNP based on the following criteria [34]:
    - Pattern of symptoms:
        i. Symptoms present for ≥12 wk;
    - Symptoms for diagnosis: Requires ≥2 of the following symptoms:
        i. Anterior and/or posterior mucopurulent drainage;
        ii. Nasal obstruction;
        iii. Facial pain/pressure/fullness;
    - Objective documentation: Requires both:
        i. Endoscopy to verify the presence of polyps in middle meatus and document presence of inflammation, such as discolored mucus or edema of middle meatus or ethmoid area; ***and***
        ii. Evidence of rhinosinusitis on imaging by CT (1 obvious polypoid tissue or sinus opacification and/or at least 2mm of mucosal thickening).
3. Failed medical management (i.e. refractory CRSwNP) and eligible for FESS.

Exclusion criteria include:

1. Contraindications to oral prednisone or known hypersensitivity to any study medications;
2. Churg Strauss disorder;
3. abnormalities of mucociliary clearance (cystic fibrosis, primary ciliary dyskinesia and Young's syndrome);
4. Diagnosed immunodeficiency.

Figure Study timeline. *Underlined text is additional steps required for this study that would not be carried out in clinical care*



This study will involve adult patients with a confirmed diagnosis of CRSwNP that is refractory to medical management and who are eligible for FESS. Patients will be seen as per the usual regimen at The University of Vermont Medical Center on the initial visit (when FESS is discussed), the day of the surgery, and follow-up at days 7 (postop week 1), 35 (5), 91 (13), 119 (17) and 182 (26, also month 6). Baseline assessments can be combined with day of surgery when applicable. These visits will be held on the mentioned days ± 5 business days to allow for accommodation of the patient's and the physicians' schedules. The procedures and outcome measurements in this study are based on the recommendations of The Rhinosinusitis Initiative (2006) which was developed by 5 national societies [34], of the Task Force on Rhinosinusitis of the American Academy of Otolaryngology-Head and Neck Surgery (1997) [35] and of The Staging and Therapy Group (1995) [36]. The administration of all tests to measure these outcomes will occur during the patients' regular visits to clinic as per current practice, necessitating more time. It will not result in any delays in treatment.

Patients will be identified by their attending physician or a resident as potential study participants. The study will be introduced to patients by the attending physician or a delegate (resident or study coordinator). If interested, patients will have the opportunity to give consent on that visit or any other day from the initial visit till the day of surgery (Day 0).

Once consent is collected, a Documentation of Consent Process will be filled by study personnel.

Each patient will have a preoperative 1 mm thick slice CT scan of the sinuses, as is standard for evaluation. CT scans will be graded according to the Lund-Mackay grading system (form 1.5) [35, 36]. Opacity of the maxillary, ethmoid, frontal and sphenoid sinuses are graded from 0-2 and the ostiomeatal complex is given a score of 0 if it is open or 2 if it is obstructed. Each side of the nose is separately evaluated and added together for a total CT score, with higher scores indicating more severe disease.

Patient who then opt for FESS as a treatment modality, will be scheduled for FESS. Those who opt not to go ahead with FESS will be withdrawn from the study.

At this point patients' baseline measurements and outcomes will be collected via answers to surveys, physical examination and lab tests. Patients' demographic data, their relevant past medical history (form 1) and their preoperative imagery score (form 1.5) will be collected from the patient at baseline. They will undergo a routine complete physical examination (form 3). Additionally, the physical exam will entail checking for anatomic variations at baseline (form 1.5), and an assessment of signs and symptoms at baseline (these are the signs and symptoms that will be monitored for medication toxicity postoperatively) using a modified version of the Common toxicity Criteria for Adverse Events (CTCAE) (form 4). A routine endoscopy scoring will be carried out using the validated Lund- Kennedy scoring scale to stage the disease [35, 36]. Patients will be asked to answer questions to one additional survey that is not usually done in practice to assess the baseline severity of their symptoms and to determine their quality of life (QOL) (form 7).

On the day of surgery, patients will undergo FESS, using a standardized perioperative protocol including preoperative administration of 10 mg of IV decadron. An intraoperative surgical staging of the patients' disease will be undertaken (form 8), along with an intraoperative collection of nasal drainage to be sent for culture. All patients will have Nasopore packing soaked in Kenalog placed in the nasal cavities.

For the first week, all patients will be instructed to take a one week oral prednisone taper and to perform normal saline intranasal sinus rinses four times daily and to use nasal saline mist every hour while awake. All patients will return to clinic approximately one week from surgery. At this visit, patients will undergo standard rigid endoscopy, scored using the Lund-Kennedy system. Any residual packing material or crusting will be debrided at that time. At this visit, patients will be randomized to one of the three study treatment groups and will be instructed to use the regimen associated with their treatment group. The three groups in this study differ with respect to the nasal rinse regimens as of this point:

1) **Steroid rinse group (control group):** the intranasal rinses will be constituted of normal saline mixed with a specific dose of budesonide (steroid) suspension;
2) **MEDIHONEY® rinse alone group (treatment group 1):** intranasal rinses will be constituted of normal saline with a specific dose of MEDIHONEY®;
3) **MEDIHONEY® and steroid rinse group (treatment group 2):** intranasal rinses will be constituted of normal saline mixed with a specific dose of budesonide (steroid) suspension and a specific dose of MEDIHONEY®;

All patients will receive instructions regarding their post-operative sinus rinse regimens. The regimens can change based on endoscopy results on the Day 91 visit as described in the Figure above and the "Drug and Device Information" section below.

Patients will be followed for a total of 26 weeks from surgery, with follow-up visits at 1, 5, 13, 17 and 26 weeks from surgery. On this and all subsequent visits, a complete physical examination (form 3), toxicity monitoring (form 4), endoscopy scoring (form 5), and SNOT-22 scoring (form 7) will be undertaken

each time. On the Day 35 visit, an additional culture of the nasal drainage will be collected and sent for analysis as done routinely.

Survey, questionnaires, etc.:

Form 1. **Demographics, history, and allergy.** This form will only need to be filled at the initial visit and necessitates 10 minutes to complete. Questions will be asked by the attending physician or delegate (study coordinator or resident) to patients. More information will be taken from the patient's routine physical examination and chart review. This form is constituted of 2 parts:

1. *Demographics:* This portion contains information collected from the patient regarding the patient's race, ethnicity, education, employment status, occupation, marital status, age and gender.
2. *Medical history:* the patient will be asked for a medical history of asthma, diabetes mellitus, smoking status and habits, history of allergy and results from allergy testing, and history of bronchiectasis.

Form 1.5. Baseline CT scan score & Anatomic Variations. This form will only need to be filled out at the initial visit, or when the CT imagery is taken, and necessitates 10 minutes to complete. The patient will need 1 hour for the CT imagery (this is already part of standard of care). This form is constituted in 2 parts:

1. *Preoperative disease computed tomography (CT) scan score:* Each patient will have a pre-operative 1 mm thick slice CT scan of the sinuses, as is standard for evaluation and required for BrainLab guidance during surgery. CT scans will be graded according to the Lund-Mackay grading system (form 1) [35, 36]. Opacity of the maxillary, ethmoid, frontal and sphenoid sinuses are graded from 0-2 and the ostiomeatal complex is given a score of 0 if it is open or 2 if it is obstructed. Each side of the nose is separately evaluated and added together for a total CT score, with higher scores indicating more severe disease. At the pre-operative visit, patients will undergo rigid nasal endoscopy which will be scored using the Lund- Kennedy scale. This scale grades nasal polyps, secretions and edema from 0-2 to gauge severity of disease.
2. *Anatomic variations:* patients will be checked during exam and by use of imagery for signs of anatomic variations. Presurgical anatomic variations in these patients will be collected via physical examination and a review of their CT scans. These variations will include septal deviation, concha bullosa, paradoxical middle turbinate, hypertrophic/curved uncinate process, pneumatized uncinate process, overpneumatized Haller cell, overpneumatized or prolabated bulla ethmoidalis, overpneumatized agger nasi cell [3, 37].

Form 3. Physical Exam. This form is from The Rhinosinusitis Initiative (2006) [34] and consists of a detailed physical examination of the head, neck and chest area. It necessitates 15 minutes to complete that is routinely performed by the attending physician or resident on all patients with CRSwNP regardless of their participation in this study.

Form 4. Toxicity monitoring. Takes 10-15 minutes to complete. Questions will be asked by the attending physician or delegate (study coordinator or resident) to patients. This form will need to be completed at all visits except on the day of surgery. Documented adverse events from the use of normal saline intranasal rinses, oral prednisone, intranasal budenoside, and MEDIHONEY® are gathered into this form. Patients will be asked baseline about these symptoms which will then be followed at the postoperative visits to monitor for medication toxicity, including the medications that are the current standard of care to compare the rates of toxicity among the different study groups. The grading for the symptoms is based on the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events version 4.0 grading system [38].

Form 5. Endoscopy score. The endoscopy (which is part of routine care at all visits) necessitates

10-15 minutes to perform and the form requires 3 minutes to complete by the attending physician or resident. This form will need to be completed at all visits except on the day of surgery. It represents the Lund-Kennedy endoscopic scoring system [36]. In 1995, the Staging and Therapy Group, headed by Valerie Lund and David Kennedy, proposed an endoscopic staging system for non-neoplastic sinonasal to evaluate therapeutic outcomes that was complex enough to incorporate the most important measures of the sinonasal cavity but simple enough to facilitate regular clinical use. Characteristics are assessed endoscopically of each sinonasal cavity to provide a score – polyp disease, mucosal edema/crusting/scarring and nasal secretion each receiving a score from 0 to 2 (form 5). This scoring system has since been the instrument of choice to endoscopically evaluate outcomes of interventions in non-neoplastic sinonasal disease prospectively over time in research and clinical practice. Endoscopy should be performed without pretreatment of any kind. If the nose is anesthetized before endoscopy, the mucous membranes are affected and the appearance of discharge and edema are altered [36]

Form 7. Sinus Questionnaire SNOT-22. Takes less than 10 minutes to complete. Questions will be asked by the attending physician or delegate (study coordinator or resident) to patients. This form will need to be completed at all visits except on the day of surgery. The SNOT-22 consists of 22 questions; items 1 to 12 represent the physical problems associated with rhinosinusitis, items 13 to 18 represent the functional limitations, and items 20 to 22 represent the emotional consequences [39]. Each question is scored by the patient from 0 (no problem) to 5 (the problem is as bad as it can be). The overall score can theoretically range from 0 to 110, with higher scores reflecting more severe quality of life impairment as subjectively reported by the patient. The twenty-two variables of SNOT-22 are: need to blow nose, nasal blockage, sneezing, runny nose, cough, post-nasal discharge, thick nasal discharge, ear fullness, dizziness, ear pain, facial pain/pressure, decreased sense of smell/taste, difficulty in falling asleep, wake up at night, lack of a good night's sleep, wake up tired, fatigue, reduced productivity, reduced concentration, frustrated/restless/irritable, sad, and embarrassed. Each symptom is rated for how "bad" it has been from 0 (no problem) to 5 (problem as bad as it can be) over the past 2 weeks (except at day 7, when it will be rated for the past week).

Form 8. Surgery score. Takes 3 minutes to complete by the attending physician or resident. Each sinus cavity and the osteomeatal complex are considered separately, with 0 awarded if no procedure was done and 1 if surgery was done [36]. The maximum score can be 0 to 14 (0 to 7 on each side).

Form 9. Post-Operative Instructions Following Endoscopic Sinus Surgery. This is a handout that will be given to all study subjects following FESS (on Day 0) and includes detailed instructions on medications, activity levels and the nasal packing. This is the usual care that is provided at UVMMC and is being handed out to patients for this study as a reminder of the instructions they will be given by the medical team post-operatively.

Form 10. Treatment group instructions. This is a handout that will be given to all study subjects on Days 7, 35, 91 and 119. It includes detailed instructions on how to prepare and perform their prescribed rinses depending on the study group, to which they have been randomized. Since the instructions change as the study progresses for each individual, the form has been created such that the research team will fill out the appropriate instructions on the abovementioned visits according to this protocol.

Primary Study Outcomes:

1) Lund-Kennedy endoscopic scores:

- In 1995, the Staging and Therapy Group, headed by Valerie Lund and David Kennedy, proposed an endoscopic staging system for non-neoplastic sinonasal to evaluate therapeutic outcomes that was complex enough to incorporate the most important measures of the sinonasal cavity but simple enough to facilitate regular clinical use. Characteristics are assessed endoscopically of each sinonasal cavity to provide a score – polyp disease, mucosal edema/crusting/scarring and nasal secretion each receiving a score from 0 to 2 [36] (form 5). This scoring system has since been the instrument of choice to endoscopically evaluate outcomes of interventions in non-neoplastic sinonasal disease prospectively over

time in research and clinical practice. Endoscopy should be performed without pretreatment of any kind. If the nose is anesthetized before endoscopy, the mucous membranes are affected and the appearance of discharge and edema are altered [36]. Endoscopy scores from the 3 study groups will be compared for the average percent change between a patient's 6 scores at the 6 different study visits (no endoscopy on day of surgery).

- *Power calculations:* Since the objective is to determine whether one treatment (MEDIHONEY® alone and MEDIHONEY® in combination with intranasal corticosteroids sinus rinses) is at least as effective or better than another control treatment (intranasal corticosteroid sinus rinses) a non-inferiority testing is needed. In the literature, patients in the control treatment at the 6 month benchmark have a 75% decrease in their endoscopy score (from 9.7 to 2.4) [40]. The standard deviation is not very clear however, so we have used a very conservative estimate based on their reporting (SD = 3.1). In order to determine whether any of the two treatment groups are at least as effective or better than this control group, with a margin of 10%, a SD of 3.1, an α of 0.25 in a one-sided test (routine for non- inferiority testing and equivalent to α of 0.05 in a two-sided test), we would need 152 patients per group for a total 456 patients. In consulting with our statistician, Dr. Peter Callas, we are aiming to enroll 10 patients per group, in order to gain a better estimate of the true SD-s. Dr. Callas thinks these numbers should be enough.

Secondary study objectives:

1) Nasal drainage cultures:

- Nasal drainage cultures from the 3 study groups will be compared for the average percent change between a patient's positive intraoperative cultures compared to the patient's cultures at day 35. Subanalyses will be done for resistant bacterial strains.

2) SNOT-22 questionnaire to assess overall quality of life [39] (modified from the SNOT-20 by Piccirillo et al [41]):

- The SNOT-22 consists of 22 questions; items 1 to 12 represent the physical problems associated with rhinosinusitis, items 13 to 18 represent the functional limitations, and items 20 to 22 represent the emotional consequences. Each question is scored by the patient from 0 (no problem) to 5 (the problem is as bad as it can be). The overall score can theoretically range from 0 to 110, with higher scores reflecting more severe quality of life impairment as subjectively reported by the patient. The twenty-two variables of SNOT-22 are: need to blow nose, nasal blockage, sneezing, runny nose, cough, postnasal discharge, thick nasal discharge, ear fullness, dizziness, ear pain, facial pain/pressure, decreased sense of smell/taste, difficulty in falling asleep, wake up at night, lack of a good sleep, wake up tired, fatigue, reduced productivity, reduced concentration, frustrated/restless/irritable, sad, and embarrassed. Each symptom is rated for how "bad" it has been from 0 (no problem) to 5 (problem as bad as it can be) over the past 2 weeks (except at day 7, when it will be rated for the past week). Overall SNOT-22 scores from the 3 study groups will be compared for the average percent change between a patient's 6 scores at the 6 different study visits (no SNOT-22 on day of surgery).

3) SNOT-22 questionnaire to assess nasal symptoms [36 & 39]:

- Assessment of symptoms is done by the patient using the above mentioned SNOTT-22 questionnaire. Total scores from the 3 study groups will be compared for the average percent change between a patient's 6 scores at the 6 different study visits (no Symptom score on day of surgery).

All other collected data, including patient demographics, anatomic variations, preop CT scan score, past medical history, and surgery score will be used for analysis purposes (potential confounding variables), and to eventually compare the population makeup of the three different groups.

Confidentiality Measures and Secure Storage of Data or Tissue:

The data in this study will consist of all the forms (1-8) which are filled and collected by the study group at the 7 different patient visits.

The aforementioned data, will be collected with identifiers including the patients' name, dates of birth,

and date/time of completion by the attending physician or a delegate (resident or study coordinator). The data will be recorded as per patients' answers, physical examination or measurements by the attending physician or a delegate. All forms for a particular patient at a particular visit will be secured as soon as the patient visit is over and will be filed in a secure, locked filing cabinet in a locked room at the OHNS clinic (ACC 4th floor).Periodically, the data will then be de-identified into Excel spreadsheets by Dr. Cairns. All patient identifiers collected during the patient visits will be de-identified before the study research team involved in data analysis has access to the information. Only the attending physicians and their designated personnel (resident or study coordinator) will have access to the identified data as they are involved in the acquisition of the data from the patients. The hard copies of the forms will be scanned into the password-protected online folder that is secure on the UVM network. The de- identified spreadsheet will be made available for data analysis purposes.

When target accrual is met, the Study Coordinators will notify the PIs, as well as the attending physicians, that the target number of subjects has been met and not to recruit further subjects. The de-identified spreadsheets will be made available to the personnel involved in the study for analysis purposes. Seven years after the research has been completed and the data have been fully processed and analyzed, the paper copies of all collected forms including Informed Consent forms will be shredded and properly disposed of along with destruction of the electronic copies.

Risks/Benefits:

The risks of participating in this study are minimal. We will not be altering the waiting time of patients receiving treatment for CRSwNP such that current standard of care is not affected. The proposed addition of MEDIHONEY® to the current standard of care is with minimal risk since it has no major adverse events documented in the literature and is nontoxic, in particular to the nasal mucosa in preclinical models [15, 16] and clinical trials [29, 32- 33] (see Toxicity section below). This is especially true for the study group in which steroids are substituted for the MEDIHONEY®. The two study groups represent situations in which a medication with a good safety profile is either added to or substitutes the current standard of care. This new medication is a natural, and nontoxic product. In both cases, the risks do not outweigh the benefits that can be gained from this study.

Determining the anticipated efficiency of MEDIHONEY® either in combination with current maintenance therapy or as a substitute is a major benefit, if true. As a natural anti-inflammatory and anti-bacterial compound, with specific efficiency against resistant strains, proving that MEDIHONEY® is as effective as or better than the standard therapy may lead to less usage of antimicrobials, which lead to resistance. In fact, a majority of CRSwNP patients with positive cultures are positive for resistant strains against which MEDIHONEY® is effective.

MEDIHONEY® does not induce resistance and is effective against resistant pathogens common in this patient population. MEDIHONEY® is also inexpensive and can be found on-the-counter.

The risk of breach of confidentiality exists with any research study. Though precautionary measures will be followed as outlined above, making such an occurrence very unlikely, any breach will be reported as per IRB guidelines.

At the time of this amendment two out of twelve participants rinsing with Medihoney product have reported the following adverse events:

1. A burning sensation
2. A stinging sensation

One participant's adverse event resolved with diluting the product in a greater amount of saline and the other participant's adverse event resolved on its own with no changes to the rinse regimen.

The potential risks in this study are justifiable as they are far outweighed by the anticipated benefits. If the anticipated results are true, the patients on MEDIHONEY® may benefit from it. Further, and whereas there are limited reports of the use of MEDIHONEY® in the literature for patients with CRS (with a subtype of CRS (namely AFRS, allergic fungal rhinosinusitis) [32] and in the first 7 days postoperatively for CRS patients [33]), there is a need for a well-designed study looking at the long-term use of MEDIHONEY® in the CRSwNP population who could benefit from such a compound with anti-inflammatory and antibacterial properties that have been studied in other contexts – mainly wound healing. This study would add to the literature and improve clinician knowledge.

Finally as a pilot study, we will gain insight into trends of benefit and the true standard deviations, based on which a full clinical trial can be designed.

Therapeutic Alternatives:

In patients with refractory CRSwNP, functional endoscopic sinus surgery, known by the acronym FESS, is intended to restore physiologic sinus ventilation and drainage, which can facilitate the gradual resolution of mucosal disease. However, because FESS does not directly treat the underlying inflammatory disorder, sinus surgery must be followed by medical management to control inflammatory processes or symptoms will invariably return [1]. Left alone, polyps usually reaccumulate within a few years without medical maintenance therapy [1, 2]. The mainstay of maintenance treatment is glucocorticoid nasal spray [3, 4] and saline irrigation [5] in all patients for 12 weeks. Oral antibiotics can also be given for a 2 week period postoperatively [2, 6]. Topical steroids have their limited but documented side effects and antibiotics can induce resistance. A semi-natural product like MEDIHONEY®, with antibacterial and anti-inflammatory properties, might prove as a useful alternative since it has no major adverse events documented in the literature, does not induce resistance and is effective against resistant pathogens common in this patient population.

Data Safety and Monitoring:

A Safety Committee comprised of Kimberly Luebbers, MSHS, RN, BSN, OCN, and Damon Silverman, MD, FACS (Associate Professor, Department of Surgery, Division of OHNS).

The study coordinators and/or Dr. Cairns will compile summaries based on the review of patients' side effects upon receipt of 15 of the Toxicity Monitoring (form 4) forms. For the safety review, the idea is to report the adverse events that reflect the time-period the patient is being treated. To achieve this, we'll start our review of the Toxicity Monitoring forms collected on Day 35 and forward. The Toxicity Monitoring forms received at baseline and Day 7 do not reflect the randomization treatment, but are equally important for the final data analysis. These summaries will document all side effects subjectively deemed by patients to be grade 3 or higher and the patients' accounts of their experience with these side effects. Study coordinators will contact patients for further clarification if needed. Such side effects will be considered as potential adverse events and reviewed by the DSM, along with patients' account of their experience. The Safety Committee will also convene after any Serious Adverse Event Form (SAFE) is received. The Safety Committee will evaluate whether there is an imbalance in incidence of side effects or adverse events, between study groups, and if any of the latter is attributable to the study. The Committee will review patient safety and any issues that surface regarding confidentiality. Any and all adverse events, including breach of confidentiality, or significant imbalance in side effects between study groups will be reported to the IRB in a timely fashion.

The Committee will also do a search midpoint and the end of the study for evidence of any new information that indicates a new or increased risk or safety issue for any of the study medications or procedures, in the form of a recent publication in the literature after IRB approval, a manufacturer report, a relevant investigator finding, revisions of medication labeling indicating an increase in the frequency or magnitude of a previously known risk, a withdrawal, restriction, or modification of a marketed approval of a

study drug, subject complaints indicating that subjects or others might be at increased risk of harm or at risk of a new harm, and/or changes significantly affecting the conduct of the study or increasing the risk to participants.

Adverse Event and Unanticipated Problem (UAP) Reporting:

The study will follow the Committees on Human Research Adverse Event and Unanticipated Problems Reporting Policy outlined in section 9B in the Manual for Human Subjects Research. Any adverse event or near miss involving a patient in this study at UVMMC will be reported according to UVMMC policy QMI00001 utilizing Fletcher Allen's electronic S.A.F.E. Reporting System.

The Safety Committee will use the following data points to monitor the incidence of adverse events in this study:

1. Any serious adverse event or near miss as per the Serious Adverse Event Form;
2. Any side effect subjectively graded by patients as grade 3 or higher as per Side Effects Forms;
3. Any breach of confidentiality.

Withdrawal Procedures:

Participation in this study is voluntary and the subject may withdraw at any time without penalty or prejudice to present and or future care. If a patient chooses to withdraw after outcomes have been collected, the data points will be kept for possible usage in data analysis. These patients will not undergo any further evaluation regarding the efficacy of the intervention without penalty.

Subjects will be withdrawn from the study if they are unable to complete the daily rinses regularly in practice, and if they opt out of surgery as a treatment method after initially being enrolled in the study. Subjects will also be withdrawn from this study in case they experience rare but major complications of FESS that would alter the patient's ability to follow the study rinsing regimens. These complications include a clinically relevant CSF leak or entry into the lamina papyrecea causing change in vision or intraocular pressure.

If a subject withdraws or is withdrawn from the study, there will be no increased risk to the patient from the medications. Subjects will be advised to follow up with their attending physician or any other physician for the best care following an interruption in participating in the study.

Sources of Materials:

Data collected from patient encounters will include: ethnicity, race, history of asthma, history of diabetes mellitus, history of smoking, history of allergy, and bronchiectasis (form 1), selective signs that are potentially present due to medication toxicity (form 4), severity of specific nasal symptoms, of CRSwNP and overall quality of life (form 7) .

Data retrieved from the patient's chart review will include: date of birth, gender (form 1), and preoperative disease CT scan score (form 1.5).

Data collected from physical examination will include: a complete physical exam of the head and neck and chest areas (form 3), presence of nasal polyps/edema/discharge/scarring/crusting (form 5), and extent of surgery (form 8).

This data will be collected specifically for the purposes of this research.

Drug and Device Information:

Manuka Honey Wound & Burn Dressing, MEDIHONEY® Wound & Burn Dressing, 3.5 fl. oz/103mL , by Derma Sciences will be provided by the company at no cost.

Budenoside (steroid) suspension, PULMICORT RESPULES®, 0.5mg/2cc suspension, by AstraZeneca. This is standard of care and will be prescribed to patients accordingly.

Oral prednisone (steroid) tablet, Deltasone®, 20mg, by Pharmacia & Upjohn. This is standard of care and will be prescribed to patients accordingly.

No placebos.

Preparation:

Patients will prepare all of the below mentioned mixtures immediately prior to use. Patients will be provided with a handout detailing instructions for these mixes. The three groups will receive the following regimens:

1. **Steroid rinse group (control group):**
    a. Days 0 till 7: Administer 40mg of oral prednisone once a day, 8oz of normal saline rinse four times a day with a saline nasal wash (e.g. NeilMed sinus rinse bottle), and intranasal saline mist spray every hour while awake;
    b. Days 7 till 91: Prepare normal saline with filtered water and salt packets. Using an 8 oz. NeilMed rinse bottle, add normal saline to the 8oz. mark. Add 1 budesonide dose. Gently swirl solution and rinse each nostril with half the solution. Administer the mixed rinse twice a day.
    c. After day 91:
        i. In case endoscopy shows any polyps, edema **or** discharge: Complete the above regimen exactly as written. Continue with this regimen till day 182.
        ii. In case endoscopy shows no polyps, edema **and** discharge: Complete the above regimen with the following changes. In the morning use 2 budesonide doses (instead of one). In the evening rinse with 8 oz. of prepared normal saline only (no budesonide) and rinse each nostril with half the solution. Reevaluate at day 119:
            1. In case endoscopy shows any polyps, edema **or** discharge: Return to the initial regimen as per 1.c.i till day 182.
            2. In case endoscopy shows no polyps, edema **and** discharge: Continue as per 1.c.ii till day 182.
2. **MEDIHONEY® rinse group (treatment group 1):**
    a. Days 0 till 7: *Same as 1.a.*;
    b. Days 7 till 91: Prepare normal saline with filtered water and salt packets. Using the 8 oz. NeilMed rinse bottle with pre-drawn MEDIHONEY line, squeeze MEDIHONEY into bottle up to the pre-drawn line. Add normal saline to the 8 oz. mark. Gently swirl solution until dissolved and rinse each nostril with half the solution Do this twice a day;
    c. After day 91:
        i. In case endoscopy shows any polyps, edema **or** discharge: Complete the above regimen exactly as written. Continue with this regimen till day 182.
        ii. In case endoscopy shows no polyps, edema **and** discharge: Complete the above regimen with the following changes. In the morning squeeze MEDIHONEY into bottle up to the 2nd pre-drawn line. In the evening rinse with 8 oz. of prepared normal saline only (no MEDIHONEY) and rinse each nostril with half the solution. Do this once a day *(instead of twice)*. Reevaluate at day 119:
            1. In case endoscopy shows any polyps, edema **or** discharge: Return to the initial regimen as per 1.c.i till day 182.

2. In case endoscopy shows no polyps, edema **and** discharge: Continue as per 1.c.ii till day 182.

3. MEDIHONEY® and steroid rinse group (treatment group 2):

a. Days 0 till 7: *Same as 1.a.*;

b. Days 7 till 91: Prepare normal saline with filtered water and salt packets. Using the 8 oz. NeilMed rinse bottle with pre-drawn MEDIHONEY line, squeeze MEDIHONEY into bottle up to pre-drawn line. Add normal saline to the 8oz. mark. Add 1 budesonide dose. Gently swirl solution until dissolved and rinse each nostril with half the solution. Do this twice a day. ;

c. After day 91:

i. In case endoscopy shows any polyps, edema **or** discharge: Complete the above regimen exactly as written. Continue with this regimen till day 182.

ii. In case endoscopy shows no polyps, edema **and** discharge: Complete the above regimen with the following changes. In the morning squeeze MEDIHONEY into bottle up to the 2nd pre-drawn line (1oz) and use 2 budesonide doses (instead of one). In the evening rinse with 8 oz. of prepared normal saline only (no MEDIHONEY and no budesonide) and rinse wach nostril with half the solution. . Reevaluate at day 119:

1. In case endoscopy shows any polyps, edema **or** discharge: Return to the initial regimen as per 3.c.i till day 182.
2. In case endoscopy shows no polyps, edema **and** discharge: Continue as per 3.c.ii till day 182.

Patients will be given clear indications as to the regimens they will need to follow. Any and all changes to their regimens (as described above) will occur following a scheduled visit, whereby the changes will be clearly explained to them.

Storage and stability:

The MEDIHONEY® and budenoside are stable and should be stored at room temperature prior to use as per the manufacturers' websites. They should be mixed with normal saline directly prior to use to ensure homogenous mixture before administration. Both will not be stored once opened such that there is no shelf life limit. The oral prednisone is also stable and should be stored at room temperature.

Toxicity:

Oral prednisone can have the following side effects: nausea, vomiting, loss of appetite, heartburn, trouble sleeping, and increased sweating. Unlikely but serious side effects include: muscle pain/cramps, irregular heartbeat, weakness, swelling hands/ankles/feet, unusual weight gain, signs of infection (such as fever, persistent sore throat), vision problems (such as blurred vision), severe stomach/abdominal pain, mental/mood changes (such as depression, mood swings, agitation), bone pain, menstrual period changes, puffy face, seizures, and easy bruising/bleeding.

This medication may infrequently increase blood sugar level rise, which can cause or worsen diabetes. A very serious allergic reaction to this product is rare, but it is advised to look for symptoms such as rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

Budenoside administered intranasally can have the following adverse side effects: epistaxis (8%), pharyngitis (4%), bronchospasm (2%), cough (2%), nasal irritation (2%). Postmarketing reports indicate immediate and delayed hypersensitivity reactions (including anaphylactic reaction, urticaria, rash, dermatitis, angioedema and pruritus), potential worsening of infections (eg, existing tuberculosis, fungal bacterial, viral, or parasitic infections; or ocular herpes simplex, chickenpox or measles), eye disorders (including glaucoma, increased intraocular pressure, cataracts), respiratory, thoracic, and mediastinal disorders (including nasal septum perforation, anosmia, pharynx disorders (throat irritation, throat pain, swollen throat, burning throat, and itchy throat), and wheezing), along with cardiac disorders (palpitations). Budenoside as a suspension in nasal rinse is expected to have even less side effects, but we will monitor

for all of the abovementioned signs and symptoms.

Normal saline nasal irrigation is safe for most adults and children when used appropriately. Some minor adverse side effects include nasal irritation or pain, otalgia, and pooled irrigant that may unexpectedly drain from the nose several minutes to hours after nasal wash. The discomfort generally abates after a few days of use.

Otalgia and pooled liquid can occur intermittently [42, 43]. Higher concentrations of saline are more likely to cause these side effects. In rare cases, some people might experience a nosebleed. None of the multiple clinical studies done note any significant adverse side effects associated with the use of nasal irrigation. Overwhelmingly, the use of nasal saline for a wide variety of sinonasal symptoms is shown to be both safe and effective.

The possible side effects of manuka honey are allergic reaction, especially in people who are allergic to bees, a rise in blood sugar and possible interaction with certain chemotherapy drugs. Most of the studies on manuka honey have been with small numbers of patients. More studies are needed to decide if it is safe and effective for various medical conditions. However in a preclinical model relevant to this study, using concentrations that are cidal against bacterial biofilms in vitro, the application of a manuka honey solution to rabbit nasal respiratory mucosa over different treatment intervals (since it is currently unknown for how long a patient would need to be treated) is safe with no evidence of histological epithelial injury [15]. Also, 3 studies in the literature have used manuka honey on the nasal mucosa with no reported toxicities [29, 32-33].

Justification for proposed use:

Derma Sciences has received FDA 510(K) clearance (K110546) for use in wound care its patented MEDIHONEY® Hydrogel Wound and Burn Dressing with Leptospermum (Manuka) honey. This product may be used without supervision for: minor abrasions, minor cuts, minor scalds, minor bums; and with supervision of a healthcare professional for: diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology), pressure ulcers / sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds.

In this study, MEDIHONEY® is being used on a surgical wound intranasally following FESS. We believe not only will the medication be useful for its intended approved action of wound healing, but that its anti-inflammatory properties might also prevent recurrence of the inflammatory hallmarks of CRSwNP: polyps, edema and discharge. Moreover, there is enough evidence for an antibacterial role that might be of benefit as well.

In this study, the route of administration is intranasal rinse of MEDIHONEY® mixed in normal saline for rinse purposes as has been done in 2 previous studies (one with a different manufacturer's product that is not FDA approved [29], and one with our same product [32]). In the latter study, the dosage form specified is very similar to our proposed dosage form.

Subject Characteristics, Identification and Recruitment:

Adult CRSwNP patients will be considered since the majority of pediatric patients with refractory to medical treatment (as per the inclusion criterion) carry a concurrent diagnosis of a mucociliary clearance disorder, namely cystic fibrosis. These patients would be excluded (as per the exclusion criterion).

The diagnosis of CRSwNP as defined in the inclusion criteria is the textbook diagnosis of this disorder. Only patients who have failed medical management, are eligible for FESS as an alternative treatment and are considering the surgery on their initial visit will be considered. This is because the study aims at determining the efficacy of different drug treatments postoperatively.

Patients who have a contraindication to the usage of oral prednisone will be excluded as this medication is used for the initial 7 days after FESS. Patients with certain comorbidities that affect the outcome of FESS in patients with CRSwNP will be excluded as well including Churg Strauss disorder, abnormalities of mucociliary and clearance (cystic fibrosis, primary ciliary dyskinesia and Young's syndrome). The treatment plan for patients with CRSwNP and these comorbidities is different from CRSwNP alone, and thus the study plan does not apply to them. Finally, patients with diagnosed immunodeficiency would not be eligible for steroid intake and will be excluded.

Number of Subjects:

A total of 40 patients. We will accrue 10 patients in each of the three study groups. The remaining 10 patients is to allow for possible study withdrawals due to various reasons such as: not electing surgery as a treatment option, having surgical complications that forego patient participation in the study, or withdrawal for any other reason once treatment has begun.

Inclusion/Exclusion Criteria:

Eligibility will be determined by attending surgeons in the Department of Surgery – Division of Otolaryngology - Head and Neck Surgery at The University of Vermont Medical Center. The physicians who oversee cases of CRSwNP are Drs. Gary Landrigan and Donald Leopold.

Inclusion criteria for patient enrollment into this study will include:

1. Age 18 years or older;
2. Diagnosis of CRSwNP based on the following criteria [34]:
    - Pattern of symptoms:
        i. Symptoms present for ≥12 wk;
    - Symptoms for diagnosis: Requires ≥2 of the following symptoms:
        i. Anterior and/or posterior mucopurulent drainage;
        ii. Nasal obstruction;
        iii. Facial pain/pressure/fullness;
    - Objective documentation: Requires both:
        i. Endoscopy to verify the presence of polyps in middle meatus and document presence of inflammation, such as discolored mucus or edema of middle meatus or ethmoid area; ***and***
        ii. Evidence of rhinosinusitis on imaging by CT (1 obvious polypoid tissue or sinus opacification and/or at least 2mm of mucosal thickening).
3. Failed medical management (i.e. refractory CRSwNP) and eligible for FESS.

Exclusion criteria include:

1. Contraindications to oral prednisone or known hypersensitivity to any study medications;
2. Churg Strauss disorder;
3. Abnormalities of mucociliary clearance (cystic fibrosis, primary ciliary dyskinesia and Young's syndrome);
4. Diagnosed immunodeficiency.

Financial Considerations:

All the processes in this study including visits, procedures, examinations, and lab testing are part

of routine care and will not be covered by the study. The only exception is the addition or substitution of MEDIHONEY® to the treatment regimens. Patients receiving MEDIHONEY® will receive the medication free of charge as its use would not be covered with medical plans. The manufacturer has agreed to provide the medication free of charge for this study's purpose.

Informed Consent:

Eligibility will be determined by attending surgeons in the Department of Surgery – Division of Otolaryngology – Head and Neck Surgery at The University of Vermont Medical Center. The physicians who oversee cases of CRSwNP are Drs. Gary Landrigan and Donald Leopold. These physicians or their delegate (a study coordinator or resident on the approved key personnel list) can solicit consent.

This is an open-label study and the patients will not be withheld any information regarding the study including the study medication which they are receiving.

A Consent Form, a Documentation of Consent Process, and a HIPAA Authorization Form will be used.

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