Stanford University
Trial Protocol (IRB-33096)

Protocol Title
The role of steroids in the perioperative management of patients with chronic rhinosinusitis: a trial protocol.

Principal Investigator
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ABSTRACT

Importance: While oral corticosteroids are commonly prescribed following endoscopic sinus surgery (ESS) for chronic rhinosinusitis, there is little data to suggest that this is a beneficial practice.

Objective: To assess the efficacy of oral corticosteroids following ESS in chronic rhinosinusitis without nasal polyposis (CRSsNP).

Design: Prospective double-blinded, placebo-controlled, randomized clinical trial

Setting: Academic tertiary rhinology practice

Participants: Adults with CRSsNP undergoing ESS.

Interventions: Patients will be randomized into two treatment groups: a 12-day postoperative taper of oral prednisone versus placebo. All study patients will also receive the a 2-week postoperative regimen of oral antibiotics, fluticasone spray, and saline rinses.

Main Outcomes and Measures: The primary outcome measures will be the Sinonasal Outcome Test 22 (SNOT-22) scores and Lund-Kennedy endoscopy scores, which will be collected preoperatively and postoperatively at 1 week, 6 weeks, 3 months, and 6 months. Scores will be compared between treatment groups at each time point using t-tests. Longitudinal difference between treatment groups was analyzed using two-way, repeated measures ANOVAs. Secondary outcome measures were side effects of corticosteroids.

Trial Registration:
Registry name: clinicaltrials.gov
Trial ID: NCT02748070
URL: clinicaltrials.gov

1. PURPOSE

A. In layperson's language state the purpose of the study in 3-5 sentences.

After patients with chronic rhinosinusitis (CRS) undergo sinus surgery, they are typically instructed to take oral steroids for several days to weeks. However, there is limited data to suggest this is a beneficial practice, and oral steroids have been shown to have significant and unpleasant side effects. This study will investigate whether there is truly evidence based utility to the use of steroids after sinus surgery.

B. State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

Chronic rhinosinusitis is a disease that affects an estimated 13% of the adult population. Patients with this disease suffer from reduced quality of life, impaired sleep, fatigue, acute infections, and chronic pain. Healthcare expenditures for CRS are estimated at $8.6 billion annually, with the majority of costs arising from repetitive physician visits, emergency department encounters, and medications. Despite its prevalence, relatively little is understood about optimal medical therapy in the post-operative period. As described above, oral steroids are routinely prescribed after sinus surgery based on anecdotal data and expert opinion rather than convincing, randomized controlled data.

The aim of conducting this study, therefore, is to to determine if oral steroids have a role in the peri-operative treatment of patients with CRS. This study would contribute a wealth of important data to the field of Rhinology and the management of CRS. The role of steroids in the peri-operative period would be further elucidated, providing randomized controlled data with which providers may make informed therapeutic decisions. In summary, the results of this study have significant potential to influence current practice and management guidelines.

C. Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

The purpose of the study is to test the efficacy of a medication in individuals with CRS, which is not a disease known to be accurately duplicated in any other model.

2. STUDY PROCEDURES

A. Please summarize the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.

Screening: Patients who have been recommended to undergo endoscopic sinus surgery by our department will be recruited for the study and informed of its purpose pre-operatively. SNOT-22 scores (a quality of life survey well established in Rhinology) and Lund-Kennedy

endoscopic exam scores (an quantitative clinical assessment of disease severity) will be recorded in their medical records. This is the same protocol performed for all patients seen in our clinic regardless of their enrollment in the study.

Randomization and Treatment Groups: The patients that wish to participate will be randomized into two treatment arms by our nurse practitioner based on a random number generator. They will receive one of the following post-operative regimens:

1) oral steroid (treatment) + steroid spray (treatment)
2) oral placebo (control) + steroid spray (treatment)

These medications will be manufactured and packaged by an independent compounding pharmacy, and prescribed by our nurse practitioner at the pre-operative visit. Patients will begin their therapy on the first post-operative day. All oral steroid regimens will be given in our institution's standard 12 days taper, while topical steroids will be delivered via a metered dose nasal spray bottle for two weeks. All study patients will receive identical peri-operative antibiotic therapy. We do not anticipate these medications to be an inconvenience to study patients as all proposed interventions are not different from routine post-operative care. In addition, patients undergoing surgery will have already trialed these medications as part of their pre-operative medical therapy.

Surgery: Routine endoscopic sinus surgery will be performed per our institution's standard protocol. In this step there will be no difference in treatment from those patients not enrolled in the study.

Post-Operative Care: At this point, patients will begin therapies according to the treatment arm to which they have been randomized. Study patients will attend post-operative appointments at identical time points to non-study patients. These will take place at the following intervals:
Post-operative visit 1: 1-2 weeks
Post-operative visit 2: 6-8 weeks
Post-operative visit 3: 3 months
Post-operative visit 4: 6 months

Experimental therapy will finish after 2 weeks. At this visit, all patients will then be maintained on intranasal steroid spray and nasal saline irrigations, which is the commonly employed therapeutic standard. Thereafter, patients will, per standard protocol, be followed on an observational basis depending on the severity of symptoms and response to treatment. At each visit, as is done for all individuals, SNOT-22 and Lund-Kennedy endoscopic exam scores will be repeated and recorded.

Statistical analyses will be performed using Stata 15 (Stata Statistical Software: Release 15; StataCorp LP, College Station, Texas). SNOT-22 and Lund-Kennedy endoscopic scores will be compared between prednisone and non-prednisone groups at each time point using t-tests. Longitudinal data will be analyzed using two-way, repeated measures ANOVAs; the within-subjects factor (Time) will be used to report changes in performance over time for the overall cohort, while the between-subjects factor (Group) will be used to report difference between

prednisone and non-prednisone groups over time. The Greenhouse-Geisser correction will be used when sphericity violations is indicated by Mauchly's test. Significance will be determined by $p < 0.05$.

B. Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

This study does not seek to evaluate a novel research procedure. Rather, we endeavor to determine if a procedure already in place nearly universally is, in fact, beneficial, as there is a distinct lack of evidence of suggest so. Overall, we are investigating a procedural method that will have fewer side effects than the currently accepted practice.

C. State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

N/A

D. State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

N/A

E. Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

All reasonable alternatives are included as a treatment arm in this study. There is no standard of care that is being withheld from patients in any group.

F. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes, patients will stop all experimental therapies at the 2 week mark. They will then be placed on the typical post-operative regimen, which includes a nasal steroid spray and twice daily saline irrigations. They will continue to be followed in our clinic after the 4 week mark, and their therapies tailored to their current symptoms and the endoscopic appearance of the nasal cavity.

G. Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the

study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?

Currently, our post-operative protocol dictates that patients will be seen in clinic at 1 week, 3 weeks, and 6 weeks after surgery. We will only slightly alter this timeline for study patients. At the 2 week appointment, all experimental therapies will be completed. Patients will then be started on intranasal steroid sprays and saline irrigations so as not to deviate for an extended period from currently accepted practices. We will use the final scheduled appointment at 4 weeks after surgery as the official end point for comparison of treatment arms.

Additionally, outcomes evaluated will be the symptom questionnaire and the endoscopic exam score at each visit. If, during the course of follow up, one regimen proves to be clearly superior to another, the study will be terminated and patients will receive the optimal therapy. By power analysis, we require 70 patients to achieve statistical significance. If there is a clearly optimal therapy determined in these first 70 patients, we will end our research at that time. All patients will continue to be followed beyond 4 weeks depending on symptom severity and response to treatment.

3. BACKGROUND

A. Describe past experimental and/or clinical findings leading to the formulation of the study.

Currently, the preferred treatment regimen for patients with chronic rhinosinusitis (CRS) with and without polyps after endoscopic sinus surgery involves a non-standardized combination of oral steroids and antibiotics. The European Position Paper on Rhinosinusitis and Nasal Polyps offers guidelines for surgeons in the appropriate therapies to improve patient symptoms based on data available in the literature to date. The use of oral steroids in CRS is associated with level IV evidence and a category C recommendation, indicating a lack of randomized controlled data to support its use (1). Therefore, this almost universal current practice is perpetuated by anecdotal data and expert opinion. Furthermore, systemic steroids are associated with known significant side effects and potential drug interactions. These may be severe and include but are not limited to high blood pressure, hyperglycemia and diabetes, adrenal suppression, weight gain, glaucoma, osteoporosis, fluid retention, gastrointestinal bleeding, ulcers, and mood changes (2). Thus, oral steroids potentially pose a significant risk, have unproven benefit, and are not appropriate for repeated or long-term use – an unfortunate obstacle in treating a chronic disease. Recently, steroids dissolved in a saline irrigant have been increasingly used and proven to be effective in the routine management of CRS. Furthermore, several studies have suggested the utility and safe side effect profile of these medications; however, the data supporting their use as a peri-operative treatment is distinctly lacking.

While the data to support the utility of topical steroids in the treatment of CRS is evident, relatively few groups have explored topical steroid irrigations specifically as a peri-operative intervention. Fandino et al conducted a meta-analysis of 13 randomized clinical trails and cohort studies examining the use of topical steroids delivered via drops, sprays, nebulizers, or irrigations for patients with CRS with nasal poylps who had previously undergone endoscopic

sinus surgery. According to his analysis, intra-nasal corticosteroids had a significant beneficial effect on symptom scores and a reduction in polyp scores.
Additionally, the use of INCS decreased the rate of polyp recurrence, and did not alter adrenocorticotropic hormones post-intervention, suggesting the intra-nasal delivery method to carry less risk than the oral version (3). Snidvongs et al conducted a study with 111 patients and reported significant improvement in symptom scores and endoscopy scores over those who did not receive post-operative topical steroids (4). Jang et al retrospectively evaluated 60 patients post-surgically who were treated with topical steroid deliveries and showed a significant decrease in quality of life and endoscopy scores after patients stopped their treatments (5).

In summary, the data supporting the use of steroids in patients with CRS immediately after endoscopic sinus surgery is sparse. We, therefore, seek to more definitively elucidate the role and utility of steroid treatment in the peri-operative period. Furthermore, per our review of the literature, there has been no direct comparison of the traditional oral regimen to topical therapy (nasal spray). Could these be proven equally effective, topically delivered steroids may be considered as a replacement for systemic steroids. This would represent a significant shift and improvement in the current post-operative management of CRS. Patients would avoid the innumerable side effects of oral steroids, which are detailed above. Furthermore, while oral steroid usage is often limited by unwanted side effects, a topical regimen may be sustained over a prolonged period as a maintenance therapy if symptoms necessitate.

State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.

Based on a current rate of 12-15 endoscopic sinus surgeries weekly, as well as allowing for a significant percentage of patients who do not desire to participate in the study, we anticipate between 80 and 100 patients to enroll. The study will be conducted only at Stanford Hospitals and Clinics. Participants will be those with CRS with and without polyps who have been recommended and consented for endoscopic sinus surgery. These participants will be used because they suffer from the specific disease for which we endeavor to research alternative therapies.

B. Describe any animal experimentation and findings leading to the formulation of the study.

None.

4. RADIOISOTOPES OR RADIATION MACHINES

N/A

5. DEVICES

N/A

6. DRUGS, REAGENTS, OR CHEMICALS

A. Please list in the table below all investigational drugs, reagents, or chemicals to be administered to participants.

N/A

B. Please list in the table below all commercial drugs, reagents, or chemicals to be administered to participants.

Drug Name	Source	IND Regulations	Manufacturer	Dosage
Prednisone	Pharmacy	Yes	West-Ward Pharmaceuticals	10-40mg
Flonase	Pharmacy	Yes	GlaxoSmithKline	50ug/dose

7. MEDICAL EQUIPMENT FOR HUMAN SUBJECTS AND LABORATORY ANIMALS

N/A

8. PARTICIPANT POPULATION

A. State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.

Based on a current rate of 12-15 endoscopic sinus surgeries weekly, as well as allowing for a significant percentage of patients who do not desire to participate in the study, we anticipate between 80 and 100 patients to enroll. The study will be conducted only at Stanford Hospitals and Clinics. Participants will be those with CRS with and without polyps who have been recommended and consented for endoscopic sinus surgery. These participants will be used because they suffer from the specific disease for which we endeavor to research alternative therapies.

B. State the age range, gender, and ethnic background of the participant population being recruited.

We will recruit patients >18 that are able to provide consent. There will be no gender or ethnic exclusions.

C. State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable

subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.

N/A

D. If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).

Children will not be included in this study as it is not typical for endoscopic sinus surgery to be performed in this population. It is rare for them to develop the extent of disease that would require surgical intervention, and surgery, in fact, is often avoided as the sinuses have not fully developed in the pediatric population. Furthermore, they are unable to provide their own informed consent to participate in this trial.

E. State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.

N/A

F. State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.

N/A

G. How will you identify and recruit potential participants about the research study? (E.g., by: chart review; notified by treating physician; response to ad). All final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may not contact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.

Recruitment will be invitation only from the patient population seen in our Rhinology clinics. Patients will first be evaluated by our providers. If, based on that evaluation, endoscopic sinus surgery is recommended to them and they meet inclusion criteria, they will then be informed of the study and its purpose and importance. After this has been discussed, patients will be invited to participate if they so choose. Our nurse practitioner performs all study introductions and obtains consent. If there are any questions, Rhinology providers are always available for consultation. We do not intend to advertise to nor recruit within the general public. There will be no recruitment materials.

H. Inclusion and Exclusion Criteria.

Inclusion criteria:
Age > 18
Able to provide informed consent
Chronic rhinosinusitis without nasal polyposis based on published diagnostic criteria
Patients undergoing endoscopic sinus surgery

Exclusion criteria:
Age <18
Aspirin exacerbated respiratory disease (also known as Samter's triad)
Allergic fungal sinusitis
Cystic fibrosis
Immunosuppression
Chronic steroid use
Steroid use within 30 days prior to surgery

I. Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).

Screening will be performed during clinic visits. First, it must be determined if a patient is a surgical candidate, which is a decision based on establishing the diagnosis of chronic rhinosinusitis by published diagnostic criteria. Furthermore, patients with this diagnosis must have failed maximum medical therapy. At the pre-operative appointment, a complete routine history will be taken as is standard in our clinics. This will include information regarding past medical history, past surgical history, current medications, social history, family history, and allergies. This information is readily available to us as a part of the electronic medical record. Patients must also confirm accuracy by filling out a questionnaire prior to their first encounter. No qualifying laboratory values are necessary.

J. Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.

We do not anticipate that participants will be enrolled in more than one study. However, we will be sure to inquire before enrolling patients if they are actively participating in another study. If so, and our interventions may interfere in any way, we will not continue with the enrollment process. We do not anticipate difficulty in recruiting the required number of patients, and, therefore, will defer to studies in which patients are already enrolled.

K. Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations

N/A

L. Costs. Please explain any costs that will be charged to the participant.

The participant will accrue identical costs to any patient being evaluated and treated for chronic rhinosinusitis, which will vary tremendously based on insurance policies. During the process, costs that may accumulate include: clinic appointments, prescribed medications, surgical intervention, specialty evaluation. No additional costs will be charged based on participation in this study.

M. Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

The study duration is anticipated to be 12-24 months. Time allotted for screening of the participant will depend heavily on the time that elapses between the initial patient encounter in clinic and the date for which surgery is scheduled. This may require 1-6 months, and occasionally longer. Active study participation will begin at the surgical date and end at the 4th post-operative visit. Organization and analysis of the data will require 2-4 weeks.

9. RISKS

A. For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the subject, it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

i. The risks of the Investigational devices.

N/A

ii. The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.

N/A

iii. The risks of the Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.

Oral Prednisone: The side effects of short courses of systemic steroids (<3 weeks) include stomach upset, weight gain, insomnia, hyperglycemia, hypokalemia, adrenal suppression, and mood changes. These can occur in up to 16% of patients, with stomach upset being the most common. These effects are all reversible after stopping the steroid.

Topical Fluticasone: The side effects of topical steroids include dry throat, sore throat, nasal irritation, headache, nose bleeds. These are the more common side effects, the incidence of which is unknown. Rare and serious side effects include difficulty breathing, flu symptoms, and vision changes. Again, these typically improve after stopping the steroids. On very rare occasion, vision symptoms may be permanent.

None of these interventions differ from those already being instituted by our staff.

iv. The risks of the Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

See the risks of the commercially available drugs - None of these interventions differ from those already being instituted by our staff.

v. The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

N/A

vi. The risks of the Physical well-being.

N/A

vii. The risks of the Psychological well-being.

N/A

viii. The risks of the Economic well-being.

N/A

ix. The risks of the Social well-being.

N/A

x. Overall evaluation of Risk.

X Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.
Medium - therapy with chemotherapy, antibodies, or a non-FDA approved potentially toxic drug, invasive procedures such some organ biopsies or catheter procedures, and some studies using biological agents
High - some organ biopsies, novel therapeutic procedures, first-time-in-humans drug or device studies, some biological agents or Recombinant DNA Vector studies

B. If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Provide an explanation as to why the research must be completed at this location and complete the International Research Form. If not applicable, enter N/A.

N/A

C. Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.

Medication administration will be monitored during the post-operative visits. Patients will begin their assigned therapy the day after surgery, and then will be seen 1, 2, and 4 weeks post-operatively. Any side effects being encountered will be discussed at these visits, and specialty services available in a timely manner to address them if needed. Furthermore, patients have 24 hour access to a physician in the department, and are, at any time, able to call with questions or concerns regarding their treatment.

Identifiable patient information will be handled per institutional protocol. Unique login information is required for all persons wishing to access the electronic medical system. All communications with patient data are sent on a secured machine via an encrypted service that is password protected.

D. Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.

The study will officially terminate for each patient after the 4th post-operative visit.

If a patient is experiencing an adverse outcome from surgery or from post-operative therapy, their participation in the study will be terminated early in the interest of well-being. In this event, patients will be promptly seen in subspecialty clinics (or by inpatient consultants if the patient is admitted to the hospital) that may assist in managing these complications. Additionally, if a patient is having an emergency, they are able to contact one of our house staff 24 hrs per day for advice. As a last resort, our Emergency Department is available for expedited work up of major events.

Finally, if it becomes clear after the first 70 patients have completed their interventional therapy that one therapy arm is drastically superior to others, and that patients are thus not receiving optimal care, the study will be terminated and therapies altered.

E. Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring. A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or

High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC. The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD). Describe the following:

1. What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?

Aggregate Data Analysis Reports
Progress toward study endpoints
AEs, SAEs, SUSARs

2. Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).

The Protocol Director will be responsible for Data and Safety Monitoring.

3. Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.

N/A

4. Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee monitoring the study in accordance with Sponsor requirements and FDA regulations.

All SAEs, SUSARs, and UPs will be reported in a timely manner in accordance with Sponsor requirements and FDA regulations.

5. If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?

N/A

6. Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.

See 2g

7. Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

Any AEs, SAEs, and UPs will be reported to the IRB, study sponsor and principal investigator. When appropriate, these will also be reported to our Risk Management group.

10. BENEFITS

A. Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.

The current standard of care in the management of CRS patients with and without nasal polyposis after endoscopic sinus surgery involves a non-standardized regimen of antibiotics and systemic steroids. However, the use of oral steroids in this period is based on anecdotal evidence and expert opinion (level IV evidence). Given the known risks of oral steroid use, it is important to definitively establish their utility and to investigate alternatives. Our study first seeks to more clearly define the role of steroids, both oral and topical, in the peri-operative setting. Furthermore, we intend to establish topical steroids as a safer but equally effective therapy. This information will be invaluable to the field and practice of Rhinology. There is a great need for additional investigation to determine whether steroids truly have a beneficial role in post-operative CRS patients. We endeavor to provide randomized, controlled data on which clinicians may base their therapeutic decisions. In addition, the introduction of topical steroids into routine post-operative care would fundamentally change current clinical practices, and may even influence future guidelines. For patients, this may transform their post-operative care into one that is more easily tolerated with less detrimental effects on health.

11. PRIVACY AND CONFIDENTIALITY

A. Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protections for follow-up interactions such as telephone, email and mail communications).

All interactions with patients will take place in a private clinical setting, which is no different from our current practice. Data collection will also be performed at this time based on the physical exam as well as a questionnaire the patient will be asked to complete in privacy while alone in the exam room. Any telephone communication will be available only via our secure electronic medical record. All e-mail will be done using electronic devices that are password

protected, backed up, and encrypted with institution specific software.

B. Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR , use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.

As during a routine medical appointment, the following will be obtained:
Name, medical record number, birthday, gender, medical history, surgical history, allergies, social history, family history.

C. You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted. See http://med.stanford.edu/datasecurity/ for more information on the Data Security Policy and links to encrypt your devices. Provide any additional information on ALL data security measures you are taking. You must use secure databases such as RedCap. If you are unsure of the security of the system, check with your Department IT representative.

No additional security measures. As stated above, all patient information will be viewed only on university provided desktops or on personal computers with institution security software installed, meaning these machines are password protected, backed up, and encrypted. Any transmissions will be done via secure, encrypted e-mail with password protected access.

D. Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.

Patient data will be labeled with an assigned numerical study code via Excel spreadsheet. This data file will be stored on our Stanford departmental server, which requires unique password log in via Stanford laptops and desktops only. The coding system file will be stored on the Study Director's Stanford issued computer which is also password protected and in a different location than the data file. There will not be de-identification of data.

E. Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).

The research team and our statistical consultant will have access to this data. Full viewing and access will be granted to the immediate research team (the Protocol Director and Academic Sponsor) so they may contribute to it as patients are seen in clinic. The statistical consultant will have read only access. All data will be managed and transmitted on secure, university provided and protected machines via secure e-mail that encrypts via Stanford specific security software.

F. If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.

Coding will be done via Excel. Each patient will be assigned a random numerical value with storage of the data file and coding file as above.

G. If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.

The Protocol Director will maintain the key to the code. The code will be contained in a separate, password protected file with an inconspicuous title. This file will exits only on the Protocol Director's Stanford issued computer, which is University compliant and password protected.

H. If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit.

Data will be shared only among the members of the research team and the statistical consultant. Transmission will be done via e-mail, including only the medical record number as identifiable patient information. All e-mails will be sent on a secured computer as an encrypted attachment that is password protected. The subject line will not refer to the content of the e-mail. Consent will be obtained from patients to use e-mail as a mode of data sharing. There will be no paper records of this data.

I. How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?

Thankfully our staff conduct many research trials and are very familiar with patient privacy protection. However, before beginning this trial we will review the HIPAA privacy guidelines for the collection and distribution of protected health information. Research staff will be reminded to access PHI only on protected computers, to log out off computers when finished, utilize private space when discussing patient or experimental data, not create any paper records that may be mistakenly left for public viewing, and to transmit data only via secure, encrypted e-mail. Finally, all involved staff will undergo their annual HIPAA renewal training in the spring of each year.

12. POTENTIAL CONFLICT OF INTEREST

All investigators declare no financial interests related to this protocol.

13. CONSENT BACKGROUND

See attached consent form.

14. ASSENT BACKGROUND (LESS THAN 18 YEARS OF AGE)

N/A

15. HIPAA BACKGROUND

Consent form contains embedded HIPAA language.

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