**Project Protocol**

**Project Title**

Comparison of the efficacy and safety of steroid-impregnated self-crosslinked hyaluronic acid (PureRegen®) and steroid-impregnated bioabsorbable polyurethane foam (Nasopore®) in adults undergoing functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis (CRS): a randomised controlled trial.

**Trial Registration/Ethics Approval**

This randomised controlled trial will be registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR) and ethics approval will be sought from the Hunter New England HREC.

**Protocol Version –** Version 3, 12th January 2021, in accordance with the SPIRIT statement

**Funding –** Nil external source of funding obtained for this study

**Investigators**

**Dr Michael Zhang MBBS (Hons)** – *Co-ordinating Principal Investigator*

Unaccredited Otolaryngology, Head and Neck Surgery Registrar/Trainee

Gosford Hospital – NSW Health Central Coast Local Health District

Email: michael.zhang@outlook.com.au

**Professor Ian Incoll FRACS MSurgicalEd MBBS***–**Principal Supervisor, Investigator*

Conjoint Professor *–* University of Newcastle

**Dr Shashinder Singh FRACS MS (ORL-HNS) MBBS** – *Supervisor, Investigator*

Head of Otolaryngology, Head and Neck Surgery

Gosford Hospital – NSW Health Central Coast Local Health District

**Dr Neil Thomson FRACS** –*Supervisor, Investigator*

Consultant Otolaryngologist, Head and Neck Surgeon

Gosford Hospital – NSW Health Central Coast Local Health District

**Associate Professor Amanda Dawson FRACS MS MMed MBBS** – *Supervisor, Associate Investigator*

Clinical Dean – Central Coast Medical School – University of Newcastle

**Dr Tony Kuo FRACS MBChB** – *Associate Investigator*

Consultant Otolaryngologist, Head and Neck Surgeon

Gosford Hospital – NSW Health Central Coast Local Health District

**Dr Indu Gunawardena FRACS MBBS** – *Associate Investigator*

Consultant Otolaryngologist, Head and Neck Surgeon

Gosford Hospital – NSW Health Central Coast Local Health District

**Dr Sebastian Ranguis FRACS MBBS BSc(Med) MM(ClinEpi) GDAAD** –*Associate Investigator*

Consultant Otolaryngologist, Head and Neck Surgeon

Gosford Hospital – NSW Health Central Coast Local Health District

**Dr James Deves FRACS –** *Associate Investigator*

Consultant Otolaryngologist, Head and Neck Surgeon

Gosford Hospital – NSW Health Central Coast Local Health District

**Background/Rationale**

Chronic rhinosinusitis (CRS) affects between 12 and 15.2% of the adult population in the United States1,2, with direct and indirect costs of management exceeding twelve billion US dollars annually2. Common treatment regimens include systemic and/or topical corticosteroids, systemic antibiotics, various adjunct therapies, with some centres also utilising novel monoclonal antibodies directed at Interleukin-5. Nasal saline irrigation has been shown to safely, cost-effectively and reliably reduce CRS symptoms, improving patients’ quality of life, with the efficacy of intranasal or systemic corticosteroids, antimicrobial and antifungal agents dependent on the severity and aetiology of a patient’s CRS3,4.

In patients whose CRS is refractory to pharmacological or medical management, functional endoscopic sinus surgery (FESS) has become a well-recognised, established and safe surgical option to re-open sinus ostia, restoring the physiological drainage pathways of the sinuses and facilitating mucociliary clearance5. This enables the thorough application of topical therapies to the sinonasal mucosa, increasing the likelihood of successful medical management6,7.

The efficacy and desirable outcomes of FESS can be reduced by postoperative inflammation, polyp recurrence and adhesions8. With recent literature associating polyp recurrence with increasing rates of revision FESS9, and published rates of polyp recurrence is as high as 70% at 18 months10, there has been research into cost-effective medical devices which can potentially reduce rates of revision by reducing postoperative scarring, adhesions and polyp recurrence. Topical steroids in the form of nasal sprays are well established in preventing these adverse outcomes11,12 and as such, there has been considerable recent investigation of intraoperative placement of bioabsorbable products to both improve and increase the longevity of the desired postoperative outcomes, thereby reducing rates of revision FESS.

To our knowledge, whether steroid-impregnated bioabsorbable synthetic polyurethane foam (Nasopore®) confers any objective or subjective postoperative benefit over steroid-impregnated self-crosslinked hyaluronic acid (PureRegen®), and the systemic and ocular safety of the use of either has not yet been studied.

**Objective**

To evaluate the efficacy and safety of steroid-impregnated self-crosslinked hyaluronic acid (PureRegen®) when compared to steroid-impregnated bioabsorbable polyurethane foam (Nasopore®) in adults undergoing functional endoscopic sinus surgery (FESS) for chronic rhinosinusitis.

**Trial Design**

Prospective, double-blinded, randomised controlled trial. 1:1 allocation between intervention groups.

**Study Setting**

Gosford Hospital, North Gosford Private Hospital

**Inclusion Criteria**

*Eligibility for FESS:*

1. CT Lund-Mackay score was ≥1, AND
2. Minimum trial of at least eight weeks’ duration of a topical intranasal corticosteroid, AND
3. Short course of systemic corticosteroid (CRSwNP) OR either a short-course of a broad spectrum / culture-directed systemic antibiotic OR the use of a prolonged course of systemic low-dose anti-inflammatory antibiotic (CRSsNP)
4. Post-medical treatment total SNOT-22 score ≥20.

*Eligibility for study:*

1. Over 18 years of age
2. Able to consent
3. Refractory to above medical treatment

**Exclusion Criteria**

*Patients with the following are ineligible for inclusion in this study:*

* Immunodeficiency
* Cystic fibrosis
* Rhinologic granulomatous disease
* Use of oral/nasal steroids from 30 days preoperatively to 30 days postoperatively
* Previous sinus surgery
* Aspirin intolerance
* Asthma
* Mucociliary disorder
* History of Glaucoma
* Unable to provide informed consent
* Unable to commit to attending follow-up appointments

**Intervention Groups**

1. Steroid-impregnated Nasopore® \*
2. Steroid-impregnated PureRegen® \*

*\* - Steroid will be Triamcinolone pending availability. An alternative liquid steroid such as budesonide may be utilised. Both steroids considered for use are TGA approved and are currently used in routine practice, and have similar safety profiles.*

**Primary Outcome**

Endoscopic appearances of sinonasal cavities at 2 weeks, 1-, 2- and 3-months post application of steroid-impregnated Nasopore® or PureRegen® as scored per the validated Lund-Kennedy and PeriOperative Sinus Endoscopy (POSE) scoring systems.

**Secondary Outcomes**

1. Systemic safety (absorption and suppression of hypothalamus-pituitary-adrenal axis) of steroid-impregnated Nasopore®/PureRegen® vs saline-impregnated Nasopore®/PureRegen® via serial measurement of early morning serum ACTH, serum cortisol (preoperatively, day 7, 14 and 28 postoperatively).
2. Ocular safety (e.g. presence of intraocular hypertension) of steroid-impregnated Nasopore®/PureRegen® vs saline-impregnated Nasopore®/PureRegen® via serial tonometry measurements (preoperatively, day 1 postoperatively, day 7, 14 and 1 month postoperatively).
3. Subjective postoperative benefit of steroid-impregnated Nasopore®/PureRegen® vs saline-impregnated Nasopore®/PureRegen® via serial SNOT-22 patient reported symptom questionnaire (preoperatively, day 14 and 1, 2, 3 month/s postoperatively).

**Hypotheses/Expected Outcomes**

The field of chronic rhinosinusitis is an ever-evolving field, with developing literature on different diagnostic modalities in evaluating emerging endotypes and phenotypes of the disease. We expect that steroid-impregnated PureRegen® will confer a greater benefit in postoperative endoscopic appearances and subjective benefit than steroid-impregnated Nasopore, with both interventions being safe from a systemic and ocular point of view.

**Methods**

60 consenting consecutive adults (120 sinuses) meeting inclusion criteria with diffuse/bilateral chronic rhinosinusitis (CRS) undergoing bilateral FESS will be randomised into two intervention groups (of 30 patients, or 60 sinuses) for inclusion. The intervention groups will be steroid-impregnated Nasopore® and steroid-impregnated PureRegen®.

Randomisation and Blinding

Randomisation will be performed using a computer-generated randomisation sequence and sealed envelopes. Trial participants will be blinded to the intervention they have received, and the outcome assessors (POSE/LK scorers) will be blinded to the intervention received. Given the nature of the interventions, the surgeon placing these interventions is unable to be blinded.

Preoperatively, patients will have their basic demographic information recorded, their early morning serum cortisol, serum ACTH, total serum IgE and a full blood count (including serum eosinophils) taken. Bilateral intraocular pressures will be measured via tonometry, and patients will be asked to complete the SNOT-22 Questionnaire. Their CT Paranasal Sinuses done as part of their workup will be evaluated and scored as per the validated Lund-Mackay scoring system.

Intraoperatively, the surgeon will record endoscopic video of the paranasal sinuses prior to performing the FESS and placing the intervention. Postoperatively, patients will be instructed to complete a one-week course of oral antibiotics (doxycycline 100mg daily) and be instructed to commence nasal saline sprays (e.g. FESS Nasal Saline Spray) from day 2 post-operatively, and saline rinses (e.g. FLO Sinus Rinse) four times a day from day 14 postoperatively.

Patients will be followed up at postoperative days 7 and 14, as well as at 1, 2, and 3 months. Endoscopic inspection will be performed at each of these visits with debridement when necessary. Endoscopic video will also be recorded for sinus assessment. All nasal dressings will be suctioned out at 14 days if not dissolved prior.

Post-operative healing assessments of oedema, crusting, secretions and scarring will be performed at these times using the validated Lund-Kennedy and Perioperative Sinus Endoscopy (POSE) scores, with subjective improvement of symptoms being assessed with the SNOT-22 score at 28 days, 1, 2 and 3 months. The assessment of the recorded endoscopic video of preoperative and postoperative sinuses will be performed by two independent consultant otolaryngologists who were not present at the initial operation, blinded to the intervention received. At day 1, 7 and 14 postoperatively, serum ACTH and serum cortisol will be collected from the patient. At day 7, 14 and 1 month, tonometry will be performed.

**Consent**

Verbal and written consent will be gained from consenting participants prior to their inclusion in the trial. Consent may be withdrawn by the participant at any time and will not affect the care they receive.

Patients who require a FESS will be consented for a FESS as per normal operating procedure. Should they further meet inclusion/exclusion criteria, they will be consented for involvement in this trial. All four arms of the trial will be explained, with a Participant Information Form provided to them for their perusal. The data required for collection will be outlined to them, and the difference between investigations that are standard procedure and investigations that are for the sole purpose of this trial will be explained.

All participants who are involved in the trial will have provided informed written and verbal consent.

**Risks**

The risks associated with being involved in this trial are minimal, and centre around the risks of the FESS surgery itself. Risks of physical and psychological harm are the same as those attributed to the FESS operation. All data is deidentified to protect privacy and no sensitive personal information is collected. There will be no economic harm to participants as participation in the trial is free, with all associated follow-up costs the same as standard patients undergoing a FESS.

The only additional risk that this trial confers is:

* Inconvenience
	+ Despite the designated follow-up times (7 days, 14 days, 1 month, 2 months, 3 months) being routine, the addition of SNOT-22 Questionnaires at 14 days, 1 month, 2 month, 3 months postoperatively represents a minor inconvenience to the patient. These questionnaires will take approximately 5 minutes on each occasion.
	+ Tonometry (painless) will be performed at each postoperative follow-up encounter – will take approximately 2 additional minutes.
* 3x Additional Blood Tests
	+ Routinely, blood is tested preoperatively, however will it also be collected on postoperative day 1, 1 week postoperatively, 2 weeks postoperatively for measurements of serum ACTH and serum cortisol.
* Incidental Findings
	+ Any incidental findings of intraocular hypertension or HPA-axis suppression will be managed by referral to the appropriate specialty.

**Benefits**

The benefits of participating in the trial is that it aims to further medical knowledge and may improve outcomes of functional endoscopic sinus surgery in the future, the longevity of the desired outcomes of functional endoscopic sinus surgery and thus reduce the rate and need of revision FESS.

The study’s benefit to each individual patient, however, is unknown, hence the reason for this trial.

**Statistical Methods**

All data will be presented in the mean +/- standard deviation format. Differences between intervention group will be assessed with a two-sample *t-test* if normally distributed, or the with the Mann-Whitney U (Wilcoxon Rank Sum) test if skewed. All differences will be presented with a 95% confidence interval, with statistical significance defined as a p < 0.05.

**References**

1. Bhattacharyya N. Contemporary Assessment of the Disease Burden of Sinusitis. *Allergy & Rhinology.* 2010;1(1):ajra.2009.2023.3355.
2. DeConde AS, Soler ZM. Chronic Rhinosinusitis: Epidemiology and Burden of Disease. American Journal of Rhinology & Allergy. 2016;30(2):134-139.
3. Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. Int Forum Allergy Rhinol. 2016;6 Suppl 1:S22-209.
4. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database of Systematic Reviews. 2007(3).
5. Lazar RH, Younis RT, Long TE. Functional endonasal sinus surgery in adults and children. The Laryngoscope. 1993;103(1):1-5.
6. Luong A, Marple BF. Sinus surgery. Clinical Reviews in Allergy & Immunology. 2006;30(3):217-222.
7. Smith TL, Batra PS, Seiden AM, Hannley M. Evidence Supporting Endoscopic Sinus Surgery in the Management of Adult Chronic Rhinosinusitis: A Systematic Review. *American Journal of Rhinology.* 2005;19(6):537-543.
8. Ramadan HH. Surgical Causes of Failure in Endoscopic Sinus Surgery. The Laryngoscope. 1999;109(1):27-29.
9. Stein NR, Jafari A, DeConde AS. Revision rates and time to revision following endoscopic sinus surgery: A large database analysis. The Laryngoscope. 2018;128(1):31-36.
10. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. The Laryngoscope. 2017;127(3):550-555.
11. Fandino M, Macdonald KI, Lee J, Witterick IJ. The use of postoperative topical corticosteroids in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. Am J Rhinol Allergy. 2013;27(5):e146-157.