STUDY PROTOCOL

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Nd:YAG Laser Photobiomodulation for Neurosensory Recovery Following Bimaxillary Orthognathic Surgery: A Randomised Sham-Controlled Double-Blinded Clinical Trial

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STUDY PROTOCOL

1. BACKGROUND AND RATIONALE

Neurosensory disturbances affecting the inferior alveolar nerve (IAN) and infraorbital nerve (ION) are well-recognised expected sequelae of bimaxillary orthognathic surgery, arising from surgical manipulation during sagittal split ramus osteotomy and Le Fort I osteotomy respectively. Persistent hypoesthesia and paresthesia affect patients' ability to speak, eat, and engage socially, and carry significant psychological burden. Current management is largely expectant, with no non-invasive adjunctive intervention supported by sham-controlled clinical trial evidence.

1.1. General Introduction

Photobiomodulation (PBM) involves application of low-energy laser irradiation to stimulate mitochondrial cytochrome c oxidase, increasing ATP production, modulating reactive oxygen species, and upregulating neurotrophic factors including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). These effects promote axonal regeneration, Schwann cell proliferation, and remyelination. The Marcos PBM M (of Fotona Lightwalker) device delivers laser irradiation transcutaneously at sub-ablative parameters within the recognised photobiomodulation therapeutic window, reaching both the IAN and ION distributions.

1.2. Rationale and justification for the Study

Developed objective neurosensory disturbance in the IAN territory confirmed by three-component composite assessment at day 5–7 postoperatively (VAS >0, Semmes-Weinstein monofilament >3.61, or static 2PD absent or >15 mm).

a. Rationale for the Study Purpose

A recent RCT (Kayim et al., 2026) comparing Nd:YAG and diode laser PBM versus no-treatment control in 30 post-orthognathic patients reported IAN functional sensory recovery (FSR) rates of 90% in laser groups versus 40% in controls (log-rank p=0.001; adjusted HR 8.04, 95% CI 2.03–31.90). No sham control was used, leaving placebo-adjusted efficacy unestablished. A 2023 systematic review and meta-analysis (Ma et al.) confirmed PBM efficacy for IAN injury recovery but noted methodological limitations including lack of sham control, inconsistent outcome measures, and absence of validated patient-reported outcomes.

b. Rationale for Doses Selected

PBM parameters (output power 0.5 W, energy density 4 J/cm², spot-by-spot application, 4-second dwell time per spot, 6 spots per side per nerve distribution) were selected based on published PBM neurosensory recovery studies and fall within the established photobiomodulation therapeutic window. Parameters are consistent with the reference study (Kayim et al., 2026) to enable direct comparison, and are within the sub-ablative range with no risk of thermal tissue effects at these settings.

c. Rationale for Study Population

Adults aged 21 years and above who develop neurosensory disturbances following bimaxillary orthognathic surgery at NUH are the target population. No upper age limit is imposed to maximise generalisability to the full adult orthognathic surgery population. The multiethnic Singapore population at NUH is specifically targeted to address the absence of Asian-population data in the existing PBM neurosensory literature.

d. Rationale for Study Design

A two-arm parallel-group RCT with double blinding (participant and outcome assessor blinded) using a sham-controlled design is selected to provide placebo-adjusted efficacy evidence. The Marcos PBM M device operates at a wavelength invisible to the naked eye; with emission deactivated in the sham arm, the device appearance, probe contact, and session duration are indistinguishable from active treatment. Cross-over design is unsuitable due to the prolonged and potentially irreversible nature of nerve regeneration. Stratified randomisation by sex and baseline IAN VAS score ensures group balance.

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

Nd:YAG laser photobiomodulation using the Marcos PBM M device (Fotona Lightwalker) will produce a statistically significant and clinically meaningful reduction in time to functional sensory recovery (FSR) in the inferior alveolar nerve (IAN) distribution compared with sham treatment at 12 months, with an acceptable safety profile.

2.2. Primary Objectives

To compare time to FSR in the IAN distribution between active PBM (Marcos PBM M) and sham treatment groups at 12 months, using a three-component composite FSR definition (VAS = 0, Semmes-Weinstein monofilament ≤3.61 detectable, and Disk-Criminator static 2PD positive at ≤15 mm).

2.3. Secondary Objectives

1. To compare 12-month FSR rates in the IAN and ION distributions between groups. 2. To compare longitudinal MRC neurosensory grade distributions (S0–S4) at each follow-up interval. 3. To compare Semmes-Weinstein monofilament thresholds and Disk-Criminator 2PD thresholds between groups at each timepoint. 4. To compare DN4 neuropathic symptom scores and OHIP-14 quality-of-life scores between groups at each timepoint. 5. To document and compare adverse events between groups.

2.4. Potential Risks and benefits:

a. End Points - Efficacy

Primary endpoint (FSR): Statistically significant reduction in median time to IAN FSR in the active group versus sham group (Kaplan-Meier log-rank $p<0.05$). FSR is defined as simultaneous achievement of: VAS = 0 in lateral IAN territory bilaterally; Semmes-Weinstein monofilament ≤3.61 detectable bilaterally; and Disk-Criminator static 2PD positive at ≤15 mm bilaterally.

b. End Points - Safety

Mild transient skin erythema at irradiation sites, self-resolving within hours. Mild warmth sensation during application. No serious adverse events anticipated based on published PBM literature at sub-ablative parameters. No thermal tissue damage, ablation, or scarring expected at 0.5 W / 4 J/cm².

3. STUDY POPULATION

3.1. Total enrolment target: 36 participants (18 per group), based on a priori power calculation (see Section 11.1). This accounts for an estimated 20% dropout rate over the 12-month follow-up period, adjusted from the minimum required sample size of 14 per group (28 total). The active treatment phase comprises 6 photobiomodulation or sham sessions delivered over 3 weeks commencing at day 5–7 postoperatively. Follow-up assessments are conducted at months 1, 3, 6, 9, and 12 post-surgery. The primary analysis will be conducted on the intention-to-treat (ITT) population. Missing outcome data will be handled by multiple imputation under the missing-at-random assumption. A per-protocol sensitivity analysis restricted to participants who completed all 6 treatment sessions and at least 4 of the 5 follow-up assessments will be conducted for the primary endpoint.
This is a single-centre study conducted at the Department of Oral and Maxillofacial Surgery, National University Hospital (NUH), Singapore. Participants will be recruited from patients undergoing bimaxillary orthognathic surgery at NUH. There are no restrictions based on race. Both sexes are eligible.

3.2. Criteria for Recruitment

Verbal consent to screening is obtained by the referring clinician. Potential participants are given the Participant Information Sheet.

3.3. Inclusion Criteria

a. Age 21-80 yearsat time of orthognathic surgery.
b. Underwent bimaxillary orthognathic surgery (SSRO and Le Fort I osteotomy), without genioplasty
c. Willing and able to comply with the full 12-month follow-up schedule comprising 12 visits.

3.4. Exclusion Criteria

a. Systemic diseases known to impair peripheral nerve regeneration, including diabetes mellitus (any type), peripheral neuropathy of any aetiology, multiple sclerosis, or other demyelinating disorders.

b. Pregnant women are excluded
c. Patients with cognitive impairment are excluded
d. History of hypersensitivity or adverse reaction to laser therapy of any type.
e. Surgical complication directly attributable to the orthognathic procedure that required reoperation or microsurgical nerve repair, as these represent a fundamentally different injury severity and recovery trajectory from the neurapraxic and axonotmetic injuries targeted by this study.
f. Genioplasty performed

3.5. Withdrawal Criteria

1. Participant request for withdrawal at any time. 2. Serious adverse event attributed to study intervention. 3. Pregnancy during the study period. 4. Investigator determination that continued participation is not in the participant's best interest. 5. Study closure by DSRB or PI.

3.6. Subject Replacement

Subjects who withdraw before the 12-month primary endpoint assessment will be replaced up to the total enrolment target of 36 (18 per group) to maintain adequate per-group numbers, subject to DSRB approval. Data from withdrawn participants will be included in the intention-to-treat analysis up to the point of withdrawal.

4. TRIAL SCHEDULE

Visits 1–6 (Weeks 0–3 post-surgery): PBM or sham sessions 2–6, twice weekly over 3 weeks. Adverse event monitoring at each session.
Visit 7 (1 month post-surgery): Full neurosensory assessment battery, DN4, OHIP-14, adverse event review.
Visit 8 (3 months post-surgery): Full neurosensory assessment battery, DN4, OHIP-14, adverse event review.
Visit 9 (6 months post-surgery): Full neurosensory assessment battery, DN4, OHIP-14, adverse event review.
Visit 10 (12 months post-surgery): Final full neurosensory assessment battery, DN4, OHIP-14, FSR determination, study exit. Sham group participants who have not achieved FSR are offered open-label PBM treatment.

5. STUDY DESIGN

This is a prospective, two-arm, parallel-group, randomised, sham-controlled, double-blinded clinical trial conducted at the Department of Oral and Maxillofacial Surgery, National University Hospital (NUH), Singapore. Two arms: (1) Active: Nd:YAG laser photobiomodulation (Marcos PBM M, 6 sessions over 3 weeks); (2) Control: Sham (device powered on, emission deactivated, identical probe application). Participants and outcome assessors are blinded to allocation. Treating operator is not blinded. Randomisation is stratified by sex and baseline IAN VAS score.

5.1. Summary of Study Design

A two-arm randomised sham-controlled double-blinded trial comparing Nd:YAG PBM (Marcos PBM M, 6 sessions, twice weekly over 3 weeks) versus sham in patients with post-orthognathic neurosensory disturbances. Primary endpoint: time to IAN FSR at 12 months by Kaplan-Meier survival analysis. Secondary endpoints: 12-month FSR rates, longitudinal MRC grading, SWM thresholds, Disk-Criminator 2PD thresholds, DN4 scores, OHIP-14 scores, adverse events. Follow-up: 12 months from surgery.

6. METHODS AND ASSESSMENTS

Procedures: (1) Baseline and follow-up neurosensory assessment (VAS with blunt 21G shaft, 5-filament Semmes-Weinstein monofilaments, Disk-Criminator static 2PD); (2) DN4 neuropathic pain questionnaire; (3) OHIP-14 oral health quality-of-life questionnaire; (4) PBM or sham laser treatment (Marcos PBM M); (5) Contralateral control site testing at every visit.

6.1. Randomisation and Blinding

Randomisation: Computer-generated block randomisation (randomly permuted block sizes of 4 and 6), stratified by sex and baseline IAN VAS score, generated by an independent biostatistician. Allocation concealment: sequentially numbered opaque sealed envelopes (SNOSE), opened only after written consent obtained. Blinding: Participants and outcome assessors blinded to allocation. Treatment operator not blinded. Marcos PBM M operates at near-infrared wavelength invisible to the naked eye; with emission deactivated in sham arm, active and sham conditions are indistinguishable to the participant. Blinding integrity assessed at month 3 using Bang Blinding Index questionnaire. Emergency unblinding permitted only where clinically essential, authorised by PI, documented and reported to DSRB within 7 days.

6.2. Contraception and Pregnancy Testing

Pregnancy during the study is a withdrawal criterion. Participants are instructed to notify the PI immediately if pregnancy is suspected.

6.3. Study Visits and Procedures

Ten visits over 13 months as detailed in the Trial Schedule section. The active treatment phase comprises visits 1–6 (First 3 weeks). Follow-up assessments at months 1, 3, 6 and 12 post-surgery.

a. Study Visits and Procedures

Day 1-21 post-surgery Treatment phase as per Trial Schedule. PBM or sham sessions at day 1-21. Neurosensory assessments at each follow-up visit (months 1, 3, 6, 12). Adverse events recorded at every visit.

b. Final Study Visit:

The final study visit occurs at 12 months post-surgery (Visit 1-). Procedures: full three-component neurosensory assessment battery, DN4, OHIP-14, final FSR determination, adverse event review, study exit. Sham group participants without FSR offered open-label PBM.

c. Post Study Follow up and Procedures

Four post-treatment follow-up visits at months 1, 3, 6 and 12 post-surgery. These visits assess neurosensory recovery trajectory. Full three-component composite assessment battery, DN4, and OHIP-14 administered at each visit. Adverse events recorded.

d. Discontinuation Visit and Procedures

If voluntary withdrawal occurs before 12 months, the participant is asked to complete a brief exit assessment (VAS, SWM, 2PD) and exit questionnaire at the point of withdrawal if willing. Data collected to date will be retained and included in the ITT analysis. The participant continues to receive standard clinical care from the treating surgical team.
If voluntary withdrawal occurs, the subject should be asked to continue scheduled evaluations, complete an end of study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable. Describe efforts to continue follow - up, especially for safety outcome measures.

7. TRIAL MATERIALS

The study uses: (1) Marcos PBM M photobiomodulation device (active treatment); (2) Marcos PBM M with emission deactivated (sham control). No drugs, implants, or other devices are used. No investigational drug is involved.

7.1. Trial Product (s)

Not applicable (Not a drug)

7.2. Storage and Drug Accountability

Not applicable (Not a drug)

8. TREATMENT

8.1. Rationale for Selection of Dose

Six PBM sessions delivered twice weekly over 3 consecutive weeks. Parameters: Marcos PBM M, confirmed device wavelength, 0.5 W output power, 4 J/cm² energy density, spot-by-spot application with calculated dwell time per spot (fluence ÷ irradiance = 4 ÷ [W/cm² from confirmed spot size]). Six anatomical spots per side per nerve distribution per session. Application time: approximately 1 minute per side (2 minutes total) per session. Parameters

selected to remain within the photobiomodulation therapeutic window per WALT dosimetry recommendations, consistent with Kayim et al. (2026).

8.2. Study Drug Formulations

PBM and sham treatment delivered in-clinic only. No devices are dispensed to participants for home use. No drugs are formulated or dispensed.

8.3. Study Drug Administration

PBM or sham sessions delivered at day 1-21, twice weekly (6 sessions total). No anaesthesia required. At each session: participant seated, wavelength-specific protective eyewear fitted for participant and operator, handpiece applied perpendicularly to skin at predefined anatomical spots along IAN and ION distributions, held for calculated dwell time per spot. In sham arm: identical procedure with emission deactivated.

8.4. Specific Restrictions / Requirements

Participants should not commence pharmacological neurotrophic agents (methylcobalamin, pregabalin, or gabapentin) for neurosensory management during the study period. All concomitant medications documented at baseline and updated at each visit.

8.5. Blinding

Participants are blinded to their treatment assignment. The sham procedure is operationally indistinguishable from active PBM: device appearance, protective eyewear, probe contact, application duration, and session scheduling are identical between arms. The Marcos PBM M operates at a near-infrared wavelength invisible to the naked eye; with emission deactivated, no audible, visible, or tactile cue distinguishes active from sham.

The outcome assessor performing all neurosensory assessments is blinded to treatment allocation throughout the 12-month follow-up. The assessor is not present during treatment sessions. The treatment operator is not involved in outcome assessment or data analysis. The biostatistician receives a dataset coded as Arm A and Arm B and remains blinded until primary analysis sign-off.

Treatment assignments generated by an independent biostatistician prior to study commencement, held by the study coordinator in SNOSE. The PI and treatment operator are informed of each participant's allocation only at the first treatment session, not at enrolment.

At the 3-month follow-up visit, participants will be asked to guess their treatment allocation as part of a blinding effectiveness assessment. The Bang Blinding Index will be calculated and reported in the published manuscript.

Full unblinding occurs after database lock following completion of the final study visit at 12 months. Each participant is informed of their treatment allocation in writing by the PI. Sham group participants are offered open-label PBM through the clinical service.

Emergency unblinding prior to 12 months may be authorised by the PI only where knowledge of allocation is clinically essential for participant safety. All unblinding events are documented and reported to the DSRB within 7 days.

8.6. Concomitant therapy

All concomitant medications, supplements, and herbal products recorded at baseline and updated at each visit. Any new medications commenced during the study are recorded with start date, dose, indication, and duration.

9. SAFETY MEASUREMENTS

9.1. Definitions

Adverse Event (AE) Any untoward medical occurrence in a study participant that occurs from the time of informed consent until the end of study participation, regardless of whether it is considered related to the study intervention. This includes new symptoms, signs, diseases, or laboratory abnormalities that were not present at baseline, or pre-existing conditions that worsen in severity or frequency during the study period.

Serious Adverse Event (SAE) Any adverse event that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death at the time of the event)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is a medically important event: an event that, based on appropriate medical judgement, may jeopardise the participant or may require intervention to prevent one of the above outcomes (e.g. severe allergic reaction not requiring hospitalisation but warranting urgent treatment)

Unexpected Adverse Event: Any adverse event whose nature, severity, or frequency is not consistent with this protocol or published PBM literature. Expected adverse events in this study include: mild transient skin erythema at irradiation sites (resolving within hours) and mild warmth sensation during application. Any adverse event beyond these expected minor effects is classified as unexpected.

9.2. Collecting, Recording and Reporting of "Unanticipated Problems Involving Risk to Subjects or Others" – UPIRTSO events to the NHG Domain Specific Review Boards (DSRB)

UPIRTSO events will be categorised according to:

1. **Unexpected**
   In terms of nature, severity or frequency of the problem as described in the study documentation (eg: Protocol, Consent documents etc).

2. **Related or possibly related to participation in the research**
   Possibly related means there is a reasonable possibility that the problem may have been caused by the procedures involved in the research; and

3. **Risk of harm**
   Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reporting Timeline for UPIRTSO Events to the NHG DSRB.

1. Urgent Reporting: All problems involving local deaths, whether related or not, should be reported immediately – within 24 hours after first knowledge by the NHG investigator.

2. Expedited Reporting: All other problems must be reported as soon as possible but not later than 7 calendar days after first knowledge by the NHG investigator.

9.3. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug must be reported to HSA.

Medical and scientific judgment will be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event will be reported as serious.

All SAEs that are unexpected and related to the study drug will be reported. The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

9.4. Safety Monitoring Plan

Given the well-established safety profile of photobiomodulation at sub-ablative parameters, a full independent DSMB is not mandated. The PI will conduct monthly safety reviews of all adverse events. A formal interim safety review will be conducted after 10 participants have completed the 6-month follow-up assessment. If ≥2 SAEs possibly related to the PBM intervention are identified, the PI will notify the DSRB and convene an independent safety review before further enrolment.

9.5. Complaint Handling –

Participant complaints are directed to the PI or study coordinator via the clinic contact number provided in the ICF. All complaints are documented, investigated, and resolved within 14 days. Unresolved complaints are escalated to the NHG DSRB. Complaint data are included in the study file.

10. DATA ANALYSIS

10.1. Data Quality Assurance

Data will be recorded on standardised reporting template. 100% source data verification will be performed by the study coordinator. Questionnaires will be checked for completeness at each visit.

10.2. Data Entry and Storage

Data will be entered on intranet medical records and transcribed into a password-protected intranet excel sheet within 7 days of collection. De-identified data only will be allowed to be used in non intra-net devices. the linking file is stored separately with restricted access. Data backed up weekly. All study data retained for 15 years per NHG policy.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

Sample size was calculated for the primary endpoint (time to IAN FSR) using the log-rank test for survival analysis in G*Power 3.1. Based on Kayim et al. (2026): assumed 12-month FSR rate 85% (active) vs 40% (sham), conservatively adjusted for the more stringent three-component composite FSR definition. Two-tailed alpha 0.05, power 80%: minimum 14 per group. Applying 20% dropout: 18 per group (36 total). Achieved power at n=18 per group exceeds 90%.
In particular, specify all of the following:

- Null and alternate hypothesis
- Type I error rate
- Type II error rate

The primary outcome measure on which sample size is based is time to IAN FSR (composite: VAS=0, SWM ≤3.61, static 2PD ≤15 mm) compared by Kaplan-Meier log-rank test between active PBM and sham groups at 12 months.
Null hypothesis (H_0): There is no difference in time to IAN FSR between the active PBM group (Marcos PBM M) and the sham control group in patients with post-orthognathic neurosensory disturbances.
Alternate hypothesis (H_1): The active PBM group demonstrates a statistically significantly shorter time to IAN FSR compared with the sham group.

The expected FSR rates (85% active vs 40% sham) were derived from Kayim et al. (2026), conservatively adjusted for the more stringent three-component composite FSR definition used in the present study. A conservative adjustment was applied because the composite criterion (requiring simultaneous achievement of VAS, SWM, and 2PD components) may reduce the observed FSR rate relative to the two-component definition used by Kayim et al.

Type I error rate: 0.05 (two-tailed).
Type II error rate: 0.20 (power 80%).

Using log-rank test for survival analysis: with FSR rates 85% vs 40%, two-tailed alpha 0.05, power 80%: minimum n=14 per group (28 total). Applying 20% dropout: n=18 per group (36 total).

11.2. Statistical and Analytical Plans

a. Primary analysis: Time to IAN FSR compared using Kaplan-Meier survival analysis, log-rank (Mantel-Cox) test. Cox proportional hazards regression to estimate hazard ratio adjusted for age, sex, and baseline IAN VAS. Proportional hazards assumption verified using Schoenfeld residuals. Secondary analyses: chi-squared or Fisher's exact test for 12-month FSR rates; GEE with ordinal logistic link for longitudinal MRC grade distributions; linear mixed models for SWM thresholds, 2PD thresholds, DN4 scores, and OHIP-14 scores. ITT primary analysis; per-protocol sensitivity analysis. Multiple imputation (20 datasets, MAR assumption) for missing data. All analyses: IBM SPSS v29.0 and R v4.4.0. Statistical significance: two-tailed $p<0.05$.
b.

c. All adverse events tabulated descriptively by group. No formal hypothesis testing for adverse event data. Blinding integrity assessed by Bang Blinding Index at month 3.

d. Interim Analyses

e. One planned interim safety review after 10 participants have completed the 6-month follow-up assessment. No efficacy interim analysis planned. No formal stopping rule for efficacy.

12. ETHICAL CONSIDERATIONS

12.1. Informed Consent

Informed consent will be obtained in accordance with the Singapore Good Clinical Practice (SGCP) guidelines, the International Council for Harmonisation Good Clinical Practice (ICH-GCP E6 R2) guidelines, and the ethical principles of the Declaration of Helsinki (2013 revision). Participation in this study is entirely voluntary. No participant will be enrolled, randomised, or subjected to any study-specific procedure before written informed consent has been obtained and documented. Participants may withdraw consent at any time without giving reasons and without prejudice to their ongoing clinical care at the National University Hospital, Singapore (NUH).

Informed consent will be obtained by anyone of the investigation team.The person obtaining consent must be knowledgeable about the study, able to answer all participant questions accurately, and have no coercive relationship with the participant. The treating clinician who delivers PBM or sham sessions may not be the sole consent-taker, to avoid any perception of therapeutic pressure.

12.2. IRB review

This protocol and the associated ICF will be submitted to the NHG Domain Specific Review Board (DSRB) for ethics approval prior to commencement of any study procedures. No participant will be enrolled before written DSRB approval is obtained. Any protocol amendments will be submitted to the DSRB for review and approval before implementation.

12.3. Confidentiality of Data and Patient Records

Participants are identified by unique study code only in all study documents and databases. The linking file (code to identity) is stored in a locked cabinet with access restricted to the PI and study coordinator. Electronic data held on NUS password-protected servers within Singapore, in compliance with the Personal Data Protection Act 2012. No biological specimens are collected. Study records retained for 15 years per NHG policy, then securely destroyed.

13. PUBLICATIONS

Results will be published in a peer-reviewed oral and maxillofacial surgery or dental journal regardless of outcome. The PI is the primary author. All investigators meeting ICMJE authorship criteria will be listed. De-identified participant data will be made available upon reasonable request after publication. The trial will be registered on ClinicalTrials.gov and clinicaltrials.sg prior to enrolment.

14. RETENTION OF TRIAL DOCUMENTS

All study records (paper CRFs, consent forms, correspondence, DSRB approvals, neurosensory assessment data, questionnaire data) will be retained for a minimum of 15 years following study completion in a secure, access-controlled location at NUH. Electronic records maintained on NUS/NUH secure servers with regular backups. Records accessible to authorised regulatory authorities (NHG DSRB, HSA, MOH) on request. At end of retention period, records destroyed per NHG data disposal policy.