**Efficacy of Hospital-Based Manufactured Medical Device Restorabite for treatment of Trismus**

**Restorabite Pivotal Trial**

**Sponsor: Chris O’Brien Lifehouse**

**Summary of Study Sites:**

|  |  |
| --- | --- |
| **Cohort Type**  | **Participating Sites** |
| Cohort 1 – Single Arm | COBLH, Wollongong Hospital  |
| Cohort 2  | COBLH, Wollongong Hospital, PMCC, KCC |
| Cohort 3 – Single Arm | COBLH only  |





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# Project Team Roles and Responsibilities

**Coordinating Principal Investigator**

**Professor Jonathan Clark, MBBS (Hons Class 1) BSc(Med) MBiostat FRACS**

Affiliations: Consultant Head and Neck Surgeon, Royal Prince Alfred Hospital and the Chris O’Brien Lifehouse; Director of Head and Neck Research, Sydney Head and Neck Cancer Institute

Address: The Chris O’Brien Lifehouse, 119-143 Missenden Road, Camperdown NSW 2050

Email: Jonathan.Clark@lh.org.au

Telephone: 02 8514 0131

Responsibilities: Professor Clark will be responsible for overall clinical conduct of research project at all sites. He will also be responsible for providing guidance on project planning, data collection and analysis, interpretation and dissemination of results, and will provide expert clinical input into the project.

## Chris O’Brien Lifehouse

**Associate Investigators**

**Dr Emma Charters, BAppSc (SpPath), Diploma of Rehabilitation, PhD Candidate**

Affiliations: Speech Pathologist, Chris O’Brien Lifehouse

Address: The Chris O’Brien Lifehouse, 119-143 Missenden Road, Camperdown NSW 2050

Email: Emma.Charters@lh.org.au

Telephone: (02) 8514 0389

Responsibilities: Ms Charters is responsible for recruitment and trismus exercises program with Restorabite at Chris O`Brien Lifehouse and for analysis and writing up research findings.

**Dr Masako Dunn, BSc(Med) (Hons Class 1) PhD**

Affiliations: Head and Neck Research Officer, Chris O’Brien Lifehouse

Address: The Chris O’Brien Lifehouse, 119-143 Missenden Road, Camperdown NSW 2050

Email: masako.dunn@lh.org.au

Telephone: 02 8514 0411

Responsibilities: Dr Dunn will be coordinating research projects at all sites. She is also responsible for data collection and management, analysis and writing up research findings.

**Ms Ashleigh Sharman, BA DipHSc BMedSc (Hons 1)**

Affiliations: Head and Neck Clinical Project Officer, Chris O’Brien Lifehouse

Address: The Chris O’Brien Lifehouse, 119-143 Missenden Road, Camperdown NSW 2050

Email: Ashleigh.Sharman@lh.org.au

Telephone: 02 8514 0413

Responsibilities: Ms Sharman will be involved in qualitative components of the research project. She will be responsible for qualitative data collection - including conducting interviews, and data management, analysis and writing up research findings.

**Researcher**

**Mr Kai Cheng, BE, M.Design (Research), PhD Candidate**

Affiliations: Royal Prince Alfred Institute of Academic Surgery and the Chris O’Brien Lifehouse

Address: The Chris O’Brien Lifehouse, 119-143 Missenden Road, Camperdown NSW 2050

Email: Kai.Cheng@health.nsw.org.au

Telephone:

Responsibilities: Mr Cheng is Surgical Innovation Research Officer who is responsible for the design, production, mechanical testing, and validation of medical device Restorabite.

## Illawarra Shoalhaven Local Health District (Wollongong Hospital)

**Principal investigator**

**A/Professor Bruce Ashford, BDSc (Hons), MBBS, PhD, FRACS**

Affiliations: Associate Professor of Surgery, Head and Neck Surgeon

Address: Building 32, University of Wollongong, Northfields Avenue, Wollongong NSW 2522

Email: bruceash@uow.edu.au

Telephone: 0242266111

Responsibilities: A/Professor Ashford will undertake overall responsibility for the operation and conduct of the clinical trial at this site. He will also be involved in protocol development and project management, analyses, writing of the manuscript and the dissemination of outcomes.

**Associate Investigator**

**Ms Jessica Boehm, BAppSc (SpPath)**

Affiliations: Speech Pathologist, ISHLD-Wollongong Hospital

Address: Level 5, Block C, Crown St, Wollongong NSW 2500

Email: Jessica.Boehm@health.nsw.gov.au

Telephone: (02) 4253 4500

Responsibilities: Ms Boehm is responsible for recruitment and trismus exercises program with Restorabite at Wollongong Hospital.

## Peter MacCallum Cancer Centre

**Principal investigator**

**Dr Jacqui Frowen, B.Sp.Path (Hons), PhD**

Affiliations: Nutrition and Speech Pathologist, Peter MacCallum Cancer Centre

Address: Locked Bag 1, A’Beckett St, Melbourne 8006

Email: jacqui.frowen@petermac.org

Telephone: 0409 133 553

Responsibilities: Dr Frowen is responsible for recruitment and trismus exercises program with Restorabite at Peter MacCallum Cancer Centre.

**Associate Investigator**

**Tess Dunlop, BAppSc (SpPath)**

Affiliations: Speech Pathologist, Peter MacCallum Cancer Centre

Address: 305 Grattan St, Melbourne, Vic, 3000

Email: tess.dunlop@petermac.org

Telephone: 8559 5221

Responsibilities: Ms Dunlop is responsible for recruitment and trismus exercises program with Restorabite at Peter MacCallum Cancer Centre.

**Associate Investigator**

**Tsien Fua, MBBS FRANZCR**

Affiliations: Radiation Oncologist, Peter MacCallum Cancer Centre

Address: 305 Grattan St, Melbourne, Vic, 3000

Email: tsien.fua@petermac.org

Telephone: 8559 7750

Responsibilities: Dr Fua is responsible for patient identification, recruitment and collection of radiation dosimetry data at Peter MacCallum Cancer Centre

## Konara Cancer Care

**Principal investigator**

**Ms Claire Jeans, B.Sp.Path**

Affiliations: Speech Pathologist, Konara Cancer Care, and GenesisCare Newcastle and Maitland; PhD Candidate, School of Health and Rehabilitation Sciences, University of Queensland

Address: Konara Cancer Care, Hunter ENT, 13 Lambton Road, Broadmeadow NSW 2292

Email: claire.hnspeechpath@outlook.com

Telephone: 0431 269 212

Responsibilities: Ms Jeans is responsible for recruitment and trismus exercises program with Restorabite at Konara Cancer Care.

## Coordinating Centre: Chris O`Brien Lifehouse

Contact for the trial:

**Professor Jonathan Clark**

Email: Jonathan.Clark@lh.org.au

Telephone: 02 8514 0268

# Summary of Changes

Protocol amendment 3.

## Cohort 1:

Cohort indicated in the version 2 of the protocol.

## Cohort 2:

### Primary Objective

Determine the optimal stretching regime for established trismus.

### Trial Design

Multi-site adaptive (2 stage) factorial (3 x 2) RCT using three levels of duration (30, 60, or 120 second (s) stretches) and two levels of maximum intensity (35 and 55 N) versus standard care as control.

**Protocol amendment 4 will include a new cohort;**

## Change 1:

### Cohort 3:

**Primary Objective**

Evaluate efficacy of Hospital-Based Manufactured Medical Device Restorabite for treatment of Trismus due to maxillofacial dysfunction following temporomandibular joint (TMJ) or orthognathic, surgery, infection, or trauma.

### Trial Design

Single arm efficacy clinical trial

Prospective, longitudinal, single site study

## Change 2:

Inclusion of clinical photos as assessment

## Change 3:

Inclusion of a semi-structured interviews for qualitative thematic analysis

# Background Information/Rationale

## Trismus

Trismus is a restriction in jaw opening experienced by 38 - 44% of people treated for head and neck cancer (1-5). It is also a common problem related to a range of diagnoses including maxillofacial dysfunction, infection, trauma, burns and brain injury.

Trismus disrupts eating, swallowing (6,7), speaking, oral care (8) and breathing. Trismus as a result of head and neck cancer is a chronic, life-long condition (9). Once onset begins, an intensive intervention program involving passive and active range and strengthening of motion is required (10,11). The impact of this is long term dental problems arising from insufficient oral care, malnutrition due to swallowing problems and loss of income due to increased frequency of medical appointments and hospital admissions. As a result of this, quality of life is diminished (7).

Despite the serious consequences of long-term trismus, research into effective interventions is inadequate. The common devices used are either make-shift devices such as Ark-J, Theraband and stacked wooden spatulas or costly devices such as Therabite and Dynasplint, which most patients do not access due to a lack of funding. There are only a handful of studies assessing the efficacy of those devices for treatment of trismus (16-23). Shao et al. reports on five studies where trismus exercises were performed using a jaw-mobilisation device. In this review, the increase in maximum interincisal opening (MIO) ranged from 4.5 mm to 14.2mm. The greatest improvements were achieved using a device named ‘EZ bite’, which is not available in Australia. The more common ‘Therabite’ had maximal gains of 10mm (21).

Surprisingly, there are no studies assessing the resistance or force applied by the available trismus devices. In most cases, the force applied to the jaw is determined by the patient and this has important implications: a) the resistance varies across therapy trials making it challenging to compare one device with another, b) there is a risk of injury if the force is excessive, particularly in the context of jaw reconstruction or poor dentition, and c) there are no guidelines for patients regarding how much force to apply, hence some patients may apply inadequate force and not achieve any therapeutic gains. Clearly, there was an unmet need to develop ***a passive and active jaw stretching device that is biomechanically validated, safe, easy to use, and affordable for trismus patients***.

Chris O`Brien Lifehouse (COBLH) and the Royal Prince Alfred Institute of Academic Surgery (RPA-IAS) have established a hospital-based 3D printing Prosthetic and Advanced Reconstructive Surgery (3D PARTS) laboratory for facial reconstruction, including prosthodontics, facial prosthetics, and the development of novel implantable devices. This laboratory has dedicated design engineers who work alongside surgeons, oncologists, and speech pathology to develop a new trismus exercise device named ‘Restorabite’. Restorabite, as per Therapeutics Good Australia (TGA) definition, is a Class I medical device. Class I medical devices are the safest type of medical device, containing non-biological material and are intended to only contact intact epithelial surfaces (skin and mucosa) and therefore do not need to be sterilised. Restorabite (Figure 1) is made of Copper3D PLACTIVE, A Copper Oxide Nanocomposite Infused PLA 3D Printer Filament. PLACTIVETM is a FDA Registered Material and EU compliant (No. 10/2011, No. 1935/2004 and No. 2023/2006).

 

*Figure 1: Restorabite kit with different coloured inserts that determine the maximum force and non-slip mouthguards that can be cleaned.*

Restorabite is unique in that it has a set maximal inter-incisal distance with different coloured inserts that provide linear resistance up to a maximum force. The forces have been quantified using an InstronTM Universal Testing Machine and the force-displacement curves are shown in Figure 2 for the various inserts. The least amount of resistance is provided by the green insert, which is designed for patients who have undergone recent surgery and using as a ‘training’ insert. The maximal resistance is provided by the red insert. The speech therapist, in conjunction with the surgeon and patient, determines when the patient is ready to graduate from one insert to the next.



*Figure 2: Force displacement curves for Restorabite inserts measured by InstronTM Universal Testing Machine.*

## Optimal stretching and strengthening regime for trismus rehabilitation

Optimal stretching and strengthening approaches for trismus rehabilitation remains unknown. This new cohort will determine the optimal stretching regime (using stretch duration and intensity variations) to increase mouth opening and a new evidence to effectively treat trismus.

# Cohort 1

## Study schema

## Diagram  Description automatically generatedObjectives/Hypothesis

### Primary Objective

Evaluate efficacy of Hospital-Based Manufactured Medical Device Restorabite for treatment of Trismus.

##

### Secondary Objective

* Improvement of interincisal distance (IID) and trismus related quality of life (QoL), for patients with head and neck cancer through use of Restorabite.
* Develop a cost-effective hospital-based manufactured biomechanically validated trismus device Restorabite.

### Hypothesis

Restorabite will produce an efficient clinical outcome measured by increase in IID and patient reported functional outcome.

## Participating Sites

Chris O`Brien Lifehouse

Illawarra Shoalhaven Local Health District (Wollongong Hospital)

## Research Plan/Study Design

### Type of Study

**Single arm efficacy clinical trial**

Prospective, longitudinal, multiple site study

### Sample Size

N = 100

Chris O`Brien Lifehouse (N=85)

Illawarra Shoalhaven Local Health District (Wollongong Hospital) (N=15)

The primary outcome of the study is to identify the increase (difference) in intercisial distance (IID) at the end of 10 week study intervention compared to the baseline. The literatures reported the IID increase of 4.5mm to 14.2mm, and the only TGA approved device Therabite reported the IID increase of 10mm. The power calculation was conducted to detect a mean IID differences of 10mm from the baseline to the end of study intervention. The study would require a sample size of 11 to achieve a power of 80% and a level of significance of 5% (two sided). The total sample size is 100 participants.

### Study duration

Start date: Date of Ethics Approval and Governance Authorisation

End date: 2 years from when first participant is enrolled

Each participant will be involved in the study minimum of 12 months

##

### Inclusion Criteria

* 18 years and older
* Diagnosis of head and neck cancer (HNC)
* Patients with an interincisal distance (IID) of 35mm or less
* Willingness to give informed consent

### Exclusion Criteria

Patients where trismus therapy is contraindicated due to medical/surgical parameters, guided by their managing physician.

##

### Assessments/Study Plan

#### Demographic and clinical data

* Primary diagnosis
* Tumour location
* Tumour classification (TNM)
* Time since treatment
* Treatment modalities (surgery, radiotherapy, chemotherapy, combination)
* Age
* Gender

#### Assessment

##### Timepoint:

Baseline, end of 10 X weekly sessions, 6 and 12 months

##### Assessment:

* + Measurement of IID
	+ Clinical photo
	+ Questionnaires
	1. Gothenburg trismus questionnaire (24)
	2. Eating assessment tool (25)
	3. Speech handicap index (26)
	4. MD Anderson dysphagia inventory (27)
	5. McGill questionnaire (short form) (28)

### Intervention

* Passive jaw range of motion exercises using Restorabite
* Active jaw range of motion exercises using Restorabite
* 10 x 1hr weekly sessions face to face or over telehealth with speech pathology. Gradual progression through the force hierarchy as clinically indicated.
* Home practice: daily for 20 minutes for duration of study.

*Note: This intervention does not differ from the standard of care of trismus, the novel part of this intervention is the use of Restorabite instead of other devices such as Ark-J.*

### Assessment of Efficacy

The efficacy of trismus treatment using Restorabite will be assessed by the increase in IID at the end of Intervention, 6 months follow up and 12 months follow up in combination with QoL measures.

* IID: This is the measure (in millimetres) between the central incisors. If the patient does not have dentition, 10mm for each set of teeth (i.e. upper missing only = subtraction of 10mm, upper and lower missing = subtraction of 20mm to measure) subtraction from the distance between the gums. This is measured by the clinician.
* Gothenburg Trismus Questionnaire: patient reported outcome measure that measures the impact of trismus on the patient’s daily life.
* Eating Assessment Tool – 10: patient reported outcome measure that enquires as to the symptoms of swallowing problems for patients
* Speech Handicap Index (SHI): patient reported outcome measure that enquires as to the impact of speech problems on a patient’s daily life
* MD Anderson Dysphagia Inventory (MDADI): patient reported outcome measure that enquires as to the impact of swallowing problems on a patient’s daily life
* McGill Questionnaire (short form): describes the sensory dimension of pain including an overall intensity measure.

# Cohort 2

## Objectives/Hypothesis

### Primary Objective

Determine optimal stretching regime for trismus treatment

### Secondary Objective

* Improvement of interincisal distance (IID) and trismus related quality of life (QoL), for patients with head and neck cancer through use of Restorabite.
* Develop a cost-effective hospital-based manufactured biomechanically validated trismus device Restorabite.

### Hypothesis

Both the duration and force applied play an important role in the treatment of trismus following oral cancer treatment.

## Participating Sites

Chris O`Brien Lifehouse

Illawarra Shoalhaven Local Health District (Wollongong Hospital)

Peter MacCallum Cancer Centre

Konara Cancer Care Broadmeadow

## Study SchemaDiagram  Description automatically generated

## Type of Study

Multi-site adaptive (2 stage) factorial (3 x 2) RCT using three levels of duration (30, 60, or 120 second (s) stretches) and two levels of maximum intensity (35 and 55 N) versus standard care as control.

The two-stage adaptive design will adopt a ‘drop-the loser’ approach where after interim analysis the least effective interventions will be abandoned to achieve full recruitment most-rapidly and minimise the number of participants exposed to ineffective interventions. If arms are dropped at interim analysis, shorter or longer durations and decreased or increased force may be substituted in the second stage if the analysis suggests this warrants exploration and is feasible.

## Sample Size

N = 20 per Arm

The maximum sample size of 280 (7 arms with 20 participants at stage 1 and 7 arms with 20 participants at stage 2) is based on a minimal detectable difference of 5 mm increase in IID, baseline mean IID of 20 mm, standard deviation 6 mm, Family-wide error rate (FWER) 0.05, power 80%, and 20% dropout rate. If futility is demonstrated at interim analysis with no dropouts, the sample size required is 112 participants.

## Study duration

Start date: Date of Ethics Approval and Governance Authorisation

End date: 2 years from when first participant is enrolled

Each participant will be involved in the study minimum of 12 months

## Inclusion Criteria

* 18 years and older
* Diagnosis of head and neck cancer (HNC)
* Patients with an interincisal distance (IID) of 35mm or less
* Willingness to give informed consent

## Exclusion Criteria

Patients where trismus therapy is contraindicated due to medical/surgical parameters, guided by their managing physician.

## Assessments/Study Plan

### Demographic and clinical data

* Primary diagnosis
* Tumour location
* Tumour classification (TNM)
* Time since treatment
* Treatment modalities (surgery, radiotherapy, chemotherapy, combination)
* Age
* Gender

### Assessment

#### Timepoint:

Baseline, end of 10 X weekly sessions, 6 and 12 months

#### Assessment:

* + Measurement of IID
	+ Clinical photo
	+ Questionnaires
	1. Gothenburg trismus questionnaire (24)
	2. Eating assessment tool (25)
	3. Speech handicap index (26)
	4. MD Anderson dysphagia inventory (27)
	5. McGill questionnaire (short form) (28)

### Intervention

* Passive jaw range of motion exercises using Restorabite as per randomised Arm
* Active jaw range of motion exercises using Restorabite as per randomised Arm
* 10 x 1hr weekly sessions face to face or over telehealth with speech pathology. Gradual progression through the force hierarchy as clinically indicated.
* Home practice: daily for 20 minutes for duration of study.

*Note: This intervention does not differ from the standard of care of trismus, the novel part of this intervention is the use of Restorabite (with defined duration and force) instead of other devices such as Ark-J.*

### Assessment of Efficacy

The efficacy of trismus treatment using Restorabite will be assessed by the increase in IID at the end of Intervention, 6 months follow up and 12 months follow up in combination with QoL measures.

### Qualitative Thematic Analysis

Optional semi-structured interviews, using an interview guide, will be conducted with patients to evaluate their experiences using a device for trismus at the end of the intervention. These 30-60minute interviews will be conducted via video conferencing (Zoom) once during the course of the trial. Interviews will be audio-recorded and transcribed verbatim for thematic analysis (Otter AI, NVivo). Please see interview guide.

With participants’ consent, direct quotes may be used in publications arising from the study. General participant consent allows the use of any de-identified quotes at the researchers’ discretion. Participants who wish to review their transcript may do so, upon request, at any time.

Interviews will be transcribed using Otter AI Transcription Software and checked for accuracy by study team members. Interview transcripts will be analysed using NVivo software. Qualitative data (interview recordings) will be analysed thematically to explore barriers and facilitators to using a device for trismus and to better understand drivers of acceptability and feasibility of such devices, within the Australian setting. All participants from cohort 2 will be invited to participate consecutively, or until saturation of qualitative themes has been reached. Optional consent for this study will be included in the participant information and consent form and the study aims to recruit 20 participants.

### Assessment

#### Timepoint:

End of 10 X weekly sessions

# Cohort 3

## Study schema

## Diagram  Description automatically generatedObjectives/Hypothesis

### Primary Objective

Evaluate efficacy of Hospital-Based Manufactured Medical Device Restorabite for treatment of Trismus due to maxillofacial dysfunction following temporomandibular joint (TMJ) or orthognathic surgery, infection, or trauma.

### Secondary Objective

* Improvement of interincisal distance (IID) and trismus related quality of life (QoL), for patients with maxillofacial dysfunction through use of Restorabite.
* Develop a cost-effective hospital-based manufactured biomechanically validated trismus device Restorabite.

### Hypothesis

Restorabite will produce an efficient clinical outcome measured by increase in IID and patient reported functional outcome.

## Participating Sites

Chris O`Brien Lifehouse

## Research Plan/Study Design

### Type of Study

**Single arm efficacy clinical trial**

Prospective, longitudinal, multiple site study

### Sample Size

N = 50 (Chris O`Brien Lifehouse)

The primary outcome of the study is to identify the increase (difference) in intercisial distance (IID) at the end of 10 week study intervention compared to the baseline. The power calculation was conducted to detect a mean IID differences of 10mm from the baseline to the end of study intervention. The study would require a sample size of 11 to achieve a power of 80% and a level of significance of 5% (two sided). The total sample size is 50 participants.

### Study duration

Start date: Date of Ethics Approval and Governance Authorisation

End date: 2 years from when first participant is enrolled

Each participant will be involved in the study minimum of 12 months

### Inclusion Criteria

* 18 years and older
* Diagnosis of maxillofacial dysfunction following temporomandibular joint (TMJ) or orthognathic surgery, infection, or trauma
* Patients with an interincisal distance (IID) of 35mm or less
* Willingness to give informed consent

### Exclusion Criteria

Patients where trismus therapy is contraindicated due to medical/surgical parameters, guided by their managing physician.

### Assessments/Study Plan

#### Demographic and clinical data

* Primary diagnosis
* Time since treatment
* Treatment modalities
* Age
* Gender

#### Assessment

##### Timepoint:

Baseline, end of 10 X weekly sessions, 6 and 12 months

##### Assessment:

* + Measurement of IID x 3 (Active pain free, Active discomfort, Passive)
	+ Clinical photo
	+ Questionnaires
		1. Gothenburg trismus questionnaire (24)
		2. Eating assessment tool (25)
		3. Speech handicap index (26)
		4. MD Anderson dysphagia inventory (27)
		5. McGill questionnaire (short form) (28)

### Intervention

* Passive jaw range of motion exercises using Restorabite
* Active jaw range of motion exercises using Restorabite
* 10 x 1hr weekly sessions face to face or over telehealth with speech pathology. Gradual progression through the force hierarchy as clinically indicated.
* Home practice: daily for 20 minutes for duration of study.

*Note: This intervention does not differ from the standard of care of trismus, the novel part of this intervention is the use of Restorabite instead of other devices such as Ark-J.*

### Assessment of Efficacy

The efficacy of trismus treatment using Restorabite will be assessed by the increase in IID at the end of Intervention, 6 months follow up and 12 months follow up in combination with QoL measures.

* IID: This is the measure (in millimetres) between the central incisors. If the patient does not have dentition, 10mm for each set of teeth (i.e. upper missing only = subtraction of 10mm, upper and lower missing = subtraction of 20mm to measure) subtraction from the distance between the gums. This is measured by the clinician.
* Gothenburg Trismus Questionnaire: patient reported outcome measure that measures the impact of trismus on the patient’s daily life.
* Eating Assessment Tool – 10: patient reported outcome measure that enquires as to the symptoms of swallowing problems for patients
* Speech Handicap Index (SHI): patient reported outcome measure that enquires as to the impact of speech problems on a patient’s daily life
* MD Anderson Dysphagia Inventory (MDADI): patient reported outcome measure that enquires as to the impact of swallowing problems on a patient’s daily life
* McGill Questionnaire (short form): describes the sensory dimension of pain including an overall intensity measure.

## Study Intervention Risks

Trismus therapy is prescribed as routine care and within the defined role of trained Speech Pathologist working with patients with head and neck cancer.

The questionnaires which are being utilised are used in routine care at present at COBLH. Some of these questionnaires (speech handicap index, MD Anderson Dysphagia inventory and McGill pain questionnaire) are about how trismus affects the patient’s quality of life. This may prompt an emotive response. Participants who experience distress related to this study will be directed to appropriate support services as required.

Although Restorabite is Class I medical device and the risk to safety is very low, the Restorabite can malfunction (frame and inserts splitting) causing damage to mouth. Adverse events will be carefully recorded and the design will be refined to reduce the risk.

Restorabite has been 3D printed with a synthetic polymer called polylactic acid (PLA). PLA has been carefully chosen for this device for its mechanical property. PLA, when it breaks, does not splinter but it splits into fibers or threads. This property ensures that 1) the breakage of device will less likely to cause a cut in the mouth, 2) the device breakage will less likely to cause the teeth/jaws to crush together, and 3) the device breakage will less likely to cause any component of the device to be projectile hitting facial structures. However, the PLA is known to fatigue over time due to a repeated use resulting in reduction in the structure integrity. This means that it is possible that the device can have reduction in the resistance force over time. The design engineer and research team have already been investigating of the possibility of using Nylon for the device, which will require a specialized Nylon 3D printer. Nylon is superior to PLA and less likely to result in the structural fatigue.

In the prototypes and clinical experience, 25 Restorabite have been tested. There have been five device breakages reported to date. No device breakage occurred during trismus exercise (study intervention) and no injury has been reported. The breakages have been reported due to researchers and participants mishandling the device or applying unnecessary forces or due to accidental breakage. All the breakage have occurred at the hinge/neck of the frame and inserts, which is furthest away from the tip of the frame where inserted into between teeth. This was an intentional product design to reduce the likelihood of an injury to mouth and teeth and have the device to fracture in controlled and predictable ways. One reported case of the device fatigue as the one insert has been used more than 30 minutes every day for over 5 weeks. The replacements have been provided to ensure a continued exercise with consistent resistance force.

The further design modifications have been applied to reduce the incidence of accidental breakage.

## Recruitment and Screening

Screening for inclusion will be carried out by the speech pathology team and Head and Neck surgeons. Treating physicians will be aware of the study and eligibility criteria, and will be able to identify potential participants at routine outpatient appointments and from their patient database. Participants can also be identified through referral from other physicians. If a potential participant is identified, they will be asked whether they would like to discuss the study and receive a copy of the Participant Information Sheet and Consent Form.  At the participants first visit the information will be discussed with them and any questions will be answered by the investigator. When the potential participants are satisfied that they understand what is involved in the study, and they have had all their questions answered to their satisfaction and they have indicated verbally that they are willing to participate they will be asked to sign the consent form with the investigator. Participants will be allowed as much time as required to consider the study and discuss the study with their family, friends or local doctor.

# Ethical Considerations

Ethics approval will be sought through the St Vincent’s Hospital, Sydney Human Research Ethics Committee. Governance approvals will be sought through the Research Governance Office at the Chris O’Brien Lifehouse and Illawarra Shoalhaven Local Health District and University of Wollongong.

## Informed Consent Process/Documentation

All participants will sign an HREC approved Participant Information Sheet and Consent Form (PISCF). Informed consent will be obtained in accordance with the Declaration of Helsinki, and local standard operating procedures/regulation prior to starting any study related procedures including screening. The written informed consent will be obtained by authorised study personnel. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations and will be approved by a Human Research Ethics Committee.

Initial contact will be made by a member of the study team as designated by the Principal Investigator, if not the Principal Investigator themselves. Information will be given in both oral and written form. The patient will be informed of the study and if interested in taking part and appear they may be eligible, they will be given a copy of the current approved PISCF to then take home and discuss with family/friend(s)/Local doctor (GP). The authorised study staff will explain the study objectives, risks and benefits, and overview of the study procedures to all participants as part of the consent process. The participant will have as much time as they require to read all of the information available and ask as many questions as they require to obtain a clear understanding of all the requirements of participating in this study, what the study involves. It will be made clear to the potential participant if they do not wish to voluntarily consent to the study or they withdraw, it would not affect their normal treatment or medical care at the institution.

##

## Confidentiality and Privacy

A unique study number will be assigned to the patient in order to maintain the patient’s privacy. The trial number will only be linked to the patient's details at the institution and will not be sent off site. The study data will be kept in coded form and will be stored in a computerised database located at Chris O’Brien Lifehouse. The investigator at each site will keep a master list that links participants to their identity, this will be stored securely and will not leave the study site. Consent to transfer data is sought via the Patient Information and Consent Form. No identifying information will be published. It is also understood that the recipients will treat the data in accordance with all applicable privacy legislation and local policies and that recipients will not use of disclose the information outside the parameters of the agreement between them and the institution. All data (including personal data) obtained will be treated as confidential. The personal data will be stored at each study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorised study staff have access.

##

## Data Storage and Record Retention

Data will be stored as coded data by allocating a unique study number for each patient. Data containing participant identifying information (including MRN, patient names) will not leave the site and only accessible by investigators. All pertaining assessment and outcome data will be stored on RedCap, a secure database which will reference the numerical code only. The data will be retained for 15 years.

# Safety and Adverse Events

## Adverse Event Definitions

In our study an adverse event will be defined as any untoward medical occurrence in a participant without regard to the possibility of a causal relationship.

## Adverse Event Recording

Adverse events will be collected after the participant has provided consent and enrolled in the study and at weekly study intervention sessions. If a participant experiences an adverse event after the informed consent document is signed (entry) but the participant has not started to receive study intervention, the event will be reported as not related to study device. All adverse events occurring after entry into the study will be recorded.

Adverse events will be recorded in database.

## Adverse Event Reporting

### Severity

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) Scale, Version 4.03 for AE grading. The CTCAE includes a grading (severity) scale for each AE term. Grades were developed using the following guidelines:

**Grade 0** – No AE or within normal limits.

**Grade 1** – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

**Grade 2** – Moderate; minimal, local or non-invasive intervention indicated.

**Grade 3** – Severe; medically significant but not immediately life threatening.

**Grade 4** – Life threatening.

**Grade 5** – Fatal.

### Relationship

The Principal Investigator (PI) at each site will be asked to document his/her opinion of the relationship of the event to the device as follows:

**Not Related**: The event is clearly related to factors other than the study device such as the subject’s clinical state.

**Possibly Related**: The event follows a reasonable temporal sequence from the time of study treatment, and/or follows a known response pattern to study device but could have been produced by other factors, such as the subject’s clinical state or other therapeutic interventions.

**Probably Related**: The event follows a reasonable temporal sequence from the time of study device and cannot be reasonable explained by other factors, such as the subject’s clinical state or therapeutic interventions.

**Definitely Related**: The event follows a reasonable temporal sequence from the time of study device, and follows a known response pattern, and cannot be reasonably explained by other factors. In addition, the event occurs immediately following study procedure(s), and/or improves on stopping the study procedure, and/or reappears on resumption of study procedure(s). These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

## Adverse Event Follow-up

All treatment-related AEs must be followed in accordance with the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements.

## Serious Adverse Events

An adverse event that meets the criteria for a serious adverse event (SAE) between study enrolments will be reported to the HREC as an SAE. If study device is discontinued as a result of an adverse event, study personnel will document the circumstances and data leading to discontinuation of treatment. A serious adverse event for this study is any untoward medical occurrence that is believed by the investigators to be causally related to study-device and results in any of the following: Life-threatening condition (that is, immediate risk of death); severe or permanent disability, or prolonged hospitalisation. Serious adverse events occurring after a participant is discontinued from the study will NOT be reported unless the investigators feel that the event may have been caused by the study device or a protocol procedure. Investigators will determine relatedness of an event to study device based on a temporal relationship to the study device, as well as whether the event is unexpected or unexplained given the participant’s clinical course, previous medical conditions, and concomitant medications.

There will be regular evaluation and monitoring of the study safety by an independent sponsor’s research committee who will review the safety profile of the medical device and participants. This committee will also review the trial progress in light of any emerging evidence which may impact the study.

# Early Termination/Withdrawal of Participants

It is not anticipated that the trial will be terminated early, however if it does so the principal investigator will inform all participants by telephone and in writing, direct correspondence to HREC and compile a final study report.

Participants who decide to withdraw from the study will be documented if verbal given or sign the withdrawal form.

# Outcomes and Future Plans

The results of the study will be published in a clinical study report which will be provided to each participating investigator once available. Overall study results will be made available to participants if they wish to receive them.

The outcomes of this research will be disseminated over multiple platforms, including publications and presentation to consumers, speech pathologists and head and neck specialists. The findings will be shared through Australian and New Zealand Head and Neck Cancer Society meetings and Speech Pathology Australia Conference, and internationally, through the Dysphagia Research Society. Our team’s relationship with existing digital media group, Head and Neck Cancer Australia’s online education platform (www.headandneckcancer.org.au), provides a unique advantage to reach a diverse, international audience.

With the efficacy of Restorabite through this study, we will present the outcome of the study to Therapeutic Goods Administration (TGA) as a clinical evidence for Class I medical device. We will apply for conformity assessment to demonstrate compliance with the Essential Principles at TGA and seek the listing of Restorabite on Australian Register of Therapeutic Goods (ARTG).

Upon the successful ARTG listing, the device might be communalised and made available in Australia. There is no potential or perceived conflict of interest of researchers, sponsors or institutions involved in this research project.

# Post-trial access to the trial intervention

If the participants receives benefit from using the device during the study they will be offered to continue treatment using the device under standard clinical management.

During the informed consent process potential participants will be informed about access to the trial intervention after study completion. This will also be explained in the HREC approved Participant Information Sheet and Consent Form.

A decision will be made in consultation between participant and the study doctor about the most appropriate treatment and follow-up arrangements for participants when this research project ends.

# Statistics

## Statistical Analysis

All data will be examined for normality. Categorical data will be presented as frequencies and percentages, and Chi Squared tests will be used to compare categorical data. QoL data will be ordinal continuous data and will be examined for normality. For data that is non-parametrically distributed the Spearman’s rho test will be used to test correlations for continuous data. For data that is parametrically distributed, the Pearson’s correlation coefficient (r) will be used to test correlations for continuous data. If conducted, post-hoc tests will be performed using the Bonferroni method to correct for multiple testing.

# Other Study Documents

|  |  |
| --- | --- |
| **Number** | **File Name** |
| 1 | Study Protocol |
| 2 | Participant Information Consent Withdrawal Form |
| Appendix A | Trismus Quality of life Questionnaire |

# Resources

Speech Pathology Australia New Research Grant and Chris O’Brien Lifehouse The SurFebruary Cancer Research Fund: Supporting seed funding for research innovation have been sought.

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