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

**Restorabite Pivotal Trial**

**Sponsor: Chris O’Brien Lifehouse**



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# Project Team Roles and Responsibilities

**Principal Investigator**

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

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Responsibilities: Professor Clark will be responsible providing guidance on project planning, data collection and analysis, interpretation and dissemination of results, and will provide expert clinical input into the project.

**Co-ordinating Investigator**

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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.

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Responsibilities: Mr Cheng is Surgical Innovation Research Officer who is responsible for the production of medical device Restorabite.

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

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Responsibilities: Dr Dunn will be responsible for data collection and management, analysis and writing up research findings.

## Coordinating Centre: Chris O`Brien Lifehouse

Contact for the trial:

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# Background Information/Rationale

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 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 to achieve any therapeutic gains. Clearly, there is 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.*

# Objectives/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

## Diagram  Description automatically generatedStudy schema

## Type of Study

**Single arm efficacy clinical trial**

Prospective, longitudinal, multiple site study

## Sample Size

N = 50

Chris O`Brien Lifehouse (N=35)

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

## 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
	+ Questionnaires
	1. Gothenburg trismus questionnaire
	2. Eating assessment tool
	3. Speech handicap index
	4. MD Anderson dysphagia inventory
	5. McGill questionnaire (short form)

### 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 millimeters) 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 cracking) causing damage to mouth. Adverse events will be carefully recorded and the design will be refined to reduce the risk.

## Recruitment and Screening

Referral to Speech Pathology, or identification via blanket referral and routine management.

Screening for inclusion will be carried out by the speech pathology team and Head and Neck surgeons.

# Ethical Considerations

Ethics approval will be sought through the Sydney Local Health District (RPA) 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. 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, prolonged hospitalisation, or a significant hazard as determined by the Data Safety Monitoring Board. 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.

# 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.

# Statistics

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 and Consent form |
| 3 | Participant Withdrawal Form  |
| Appendix A | Trismus Quality of life Questionnaire |

# Resources

Speech Pathology Australia New Research Grant has been sought.

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