



CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:

3D Printed Scaffold Device for Ridge Preservation after Tooth Extraction – A Randomised Controlled Clinical Trial

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LIST OF ACRONYMS

3D – 3 Dimensional

ASA - American Society of Anesthesiologists

AE – Adverse Event

BV – Bone Volume

CIRB – Centralized Institutional Review Board

CRF – Case Report Form

CT - Computed Tomography

DFDBA - Demineralized freeze-dried bone allograft

FDA - Food and Drug Administration

FDM - Fused Deposition Modelling

HSA – Health Science Authority

ISQ - Implant Stability Quotient

NDCS – National Dental Centre Singapore

NTU – Nanyang Technological University

OI – Osteopore International

OPG – Orthopantomogram

PCL TCP - Polycaprolactone – tricalcium phosphate

PCL – Polycaprolactone

RFA – Resonance Frequency Analysis

RHmeb– Ridge height mesio-buccal

RHmib – Ridge height mid-buccal

RHdb – Ridge height disto-buccal

RW – Ridge Width

SAE – Serious Adverse Event

TCP - Tricalcium phosphate

PROTOCOL SIGNATURE PAGE

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Protocol Number: 252/2017

Protocol Version/ Date: Version 2/ 15 March 2018

Sponsor Name: Osteopore International (Singapore) Pte Ltd

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP)

Principal Investigator Name: Cl A/Prof Goh Bee Tin



Principal Investigator Signature: _____

Date: 20/3/18 _____

1 BACKGROUND AND RATIONALE

Dental implant-supported prostheses are fast gaining popularity as the treatment of choice for tooth replacement. Dental implants and their respective parts and tools have become the fastest growing area in dentistry and the dental supply industry. The basis for modern dental implants (endosseous implant) is a biologic process called osseointegration, which refers to a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant. The long-term success of dental implants, in terms of clinical stability and aesthetic result of the prosthesis, is dependent on the dental implant being supported by adequate amount of bone in the alveolar ridge.

Following tooth extraction, the socket usually heals naturally with bone tissue in 1 to 2 months¹⁻³. This healing process, however, occurs with substantial reduction of the original height and width of the alveolar ridge (Figure 1). Most of the dimensional alterations occur in the first 2 to 3 months after tooth extraction^{4,5}. In a systematic review, a reduction of 3.87 mm and 1.67 mm in alveolar bone width and height respectively within 3 months after dental extraction was reported⁶. Another systematic review reported vertical dimensional change of 11 - 22 % and a horizontal dimensional change of 29 - 63% in the alveolar ridge at 6 months after dental extraction⁷. Bone resorption is more pronounced on the buccal than the palatal/ lingual aspect of the ridge^{5,8,9}. The resultant effect of this resorption pattern is transportation of the diminished ridge to a more palatal or lingual position.



Figure 1: Bone resorption after tooth extraction resulting in reduction in ridge height and width

In a significantly resorbed ridge, bone augmentation procedures are necessary before surgical dental implant placement. Currently, autogenous bone is considered the gold standard as a graft material for this purpose. The bone may be harvested from various locations, such as the mandibular ramus, chin, iliac crest or calvarium, depending on, among other factors, the quantity of bone required. This implies that the patient is subjected to additional surgery and its associated morbidities and expenses. The cost of autogenous bone augmentation surgery ranges from about SGD\$1350 (e.g. mandibular or chin donor site) to about SGD\$8000 (e.g. iliac crest donor site, requiring an average of 4 days hospital stay). Patients seeking dental treatment are often expecting simple and less invasive solutions and are often unwilling to undergo complicated and expensive surgery.

To counteract alveolar ridge resorption after extraction, “ridge preservation” techniques have been introduced^{9,10}. Ridge preservation is defined as any procedure undertaken at the time of or following an extraction that is designed to minimise external resorption of the ridge and maximise bone formation within the socket¹¹. For this purpose, xenografts, allografts and/ or synthetic materials used alone or in conjunction with a membrane have been used to fill the tooth socket. Among the various materials available¹²⁻¹⁸, bovine porous bone mineral¹² and demineralised freeze-dried bone allograft (DFDBA)¹³⁻¹⁵ are the most commonly used. While studies have shown these materials to be effective in preserving ridge dimensions to some extent^{19,20}, they **failed to prevent vertical resorption of the buccal and palatal bony walls**²¹. Their osteoconductivity is suboptimal and unpredictable and the graft materials often interfered with the normal healing process^{13-15,22}. Sites grafted with a bovine bone mineral Bio-Oss[®] were found to comprise of connective tissue and only 40% of the circumference of the Bio-Oss[®] particles was in contact with woven bone²³. Another study using DFDBA showed no evidence of bone formation on

the surfaces of the non-viable particles¹³. Several other investigators have demonstrated the presence of graft particles in alveolar sockets for as long as 6 to 9 months following insertion^{12,15,24,25} and they may not be fully replaced by host bone even after a prolonged period of healing. The use of xenografts and allografts also subjects the patient to small risks of disease transmission and adverse immune reaction and their use may not be acceptable for certain religions or cultures.

Cost of bone substitutes:

Bone substitute	Price (SGD)
<u>Xenograft</u>	
Bio-Oss® 0.25g	\$139
Bio-Oss® 0.50g	\$201
<u>Allograft</u>	
Puros® 0.5cc	\$220
Puros® 1.0cc	\$303
Puros® 2.0cc	\$482

Market Size

Dental implant and bone augmentation surgeries are commonly performed procedures in Singapore and globally. **The market size and potential for growth are tremendous.** According to business report provider GBI Research, the global dental implants market is expected to grow at a compound rate of 10 percent from \$3.4 billion in 2011 to \$6.6 billion in 2018. The rapid growth is driven by the ageing population worldwide as well as technological advancements that have markedly improved dental implant treatment efficiency and success rate (Dental Tribune International 11 Feb 2013). According to another report from research and consulting firm GlobalData, the global bone grafts and substitutes market value will similarly increase steadily over the coming years, rising from almost \$2.1 billion in 2013 to approximately \$2.7 billion by 2020, at a compound rate of 3.8% (GlobalData 29 Jan 2014).

Unpublished data estimated that 15,000 dental implants are being inserted in patients per year in Singapore.

1.1 General Introduction

To meet the clinical need of maintaining bone volume and contour of the alveolar ridge following tooth extraction, we propose the solution of using a novel 3-dimensional (3D) printed polycaprolactone – tricalcium phosphate (PCL-TCP) bioresorbable scaffold device for ridge preservation.

Polycaprolactone (PCL) is a bioresorbable polymer and is regarded as a non-toxic and tissue-compatible material²⁶. It has been used in many medical devices for the last 30 years such as Capronor™, a one-year implantable subdermal contraceptive device²⁷ and Monocryl™ a resorbable monofilament suture²⁸. Both are Food and Drug Administration (FDA)-approved clinical products. More recently it has been approved as a bone filler for craniofacial applications (510K FDA K051093) (http://www.accessdata.fda.gov/cdrh_docs/pdf5/K051093.pdf). The PCL scaffold is intended for use in the repair of neurosurgical burr holes, craniotomy cuts and other cranial defects and in the augmentation or restoration of bony contour in the craniofacial skeleton²⁹. An interdisciplinary group, then at the National University of Singapore led by Prof Teoh Swee Hin, in collaboration with Temasek Polytechnic, evaluated and patented the parameters used to process PCL and PCL composites by an Additive Manufacturing or 3D printing technique known as Fused Deposition Modelling (FDM)³⁰. The unique feature of these FDM scaffolds lies in the 3-angle layering (0°/60°/120°) that results in a fully

interconnected matrix architecture that provides maximum anchorage for cell attachment³⁰⁻³². The scaffold has mechanical properties closely similar to bone, exhibits slow degradation kinetics, enhances blood clot entrapment and vascular ingrowth and is osteoconductive. PCL products manufactured and commercialized by Osteopore International (OI) include the OsteoPlug™ for the repair of neurosurgical burr holes as well as the OsteoMesh™ and OsteoStrip™ for orbital floor reconstruction.

The second-generation scaffolds produced by FDM are based on composites. Bioactive composite 3D scaffolds comprising of a biodegradable polymeric phase (e.g. PCL) and a bioactive phase (e.g. TCP) that can bond spontaneously to and integrate with bone are recent innovations in the field of regenerative medicine. It was hypothesized that PCL-TCP scaffolds possess cell and protein binding sites due to the nucleation of TCP on its surface^{33,34}. The PCL-TCP scaffold was shown to have improved mechanical and biochemical properties compared to the first generation PCL scaffolds³⁵⁻³⁷. The incorporation of TCP into a PCL polymer matrix allows tailoring the desired degradation kinetics of the scaffold. PCL scaffolds degrade at a slow rate due to its high molecular weight and hydrophobicity. The added TCP particles, being hydrophilic, are dislodged from the PCL matrix during degradation and interact with the surrounding body fluid shortly after implantation. The dislodgement of TCP creates voids within the polymer, thus exposing their surfaces to hydrolytic attack and weakening the overall structure of the PCL. By this mechanism, the addition of TCP accelerates the degradation of the PCL polymer.

The scaffold to be used in this study was co-designed by the bioengineering team from the School of Chemical and Biomedical Engineering, NTU, led by Prof Teoh Swee Hin and the Oral and Maxillofacial Surgery team from the NDCS, led by Dr Goh Bee Tin. The scaffold is conical in shape and available in 2 different sizes. The small size (5 mm diameter) is suitable for use in incisor, canine and premolar tooth sockets while the large size (8 mm diameter) is suitable for use in molar tooth sockets. The unique physical properties of the PCL-TCP scaffold allow it to be easily shaped intra-operatively by cutting and shaving with a scalpel to fit each individual socket snugly. Customization is therefore not necessary, saving production time and cost. The PCL-20% TCP scaffolds will be manufactured by OI using the latest FDM techniques (FDM 3000; Stratasys, Eden Prairie, MN), in a class 10K clean room environment. Each scaffold will have a lay-down pattern of 0°/60°/120° and porosity of 70%. The PCL-TCP scaffold will have a typical honeycomb structure with interconnected equilateral triangles of regular porous morphology. It will be individually packed and sterilized using gamma irradiation.

The xenograft, allograft and synthetic materials currently available in the market for this application are mostly granular or particulate in form that lacks a 3D structural shape. We postulate that the 3D shape of the PCL-TCP scaffold device that can be fashioned intraoperatively to fit snugly within the tooth socket will be more effective as a space maintainer during bone healing that favours maintenance of ridge dimensions and contour (Figure 2). Results of a pilot clinical trial conducted by our group showed that the use of a PCL scaffold for ridge preservation resulted in statistically significant less vertical ridge resorption compared to a control group where no scaffold was used³⁸. Moreover, both the fully interconnected porosity that enhances cell attachment, as well as the bioactivity of the TCP component promote osteogenesis. Previous studies by our group showed direct contact between newly formed bone and the PCL or PCL-TCP struts, with no connective tissue interface^{38,39}. Another major advantage of the PCL-TCP scaffold over the currently commonly used xenografts and allografts is that, being synthetic, it is available in unlimited quantity and its manufacturing technique using FDM is relatively inexpensive. When mass produced in the future, the PCL-TCP scaffold can be marketed at a much lower cost (estimated between SGD\$80 – 100) than materials derived from animal or cadaveric sources. Needless to say, the PCL-TCP scaffold also does not pose any danger of disease transmission and is more likely to be accepted by different cultures and religions.

1.2 Rationale and Justification for the Study

Include a description and justification for the route of administration, dosage, dosage regimen, intervention periods, and selection of study population. Include a statement of hypothesis.

The research hypothesis is that the insertion of a 3D bioresorbable PCL-TCP scaffold in fresh extraction sockets allows for normal bone healing and less resorption of the alveolar ridge after 6 months compared to the resorption in extraction sockets without any space filler.

1.2.1 Rationale for the Study Purpose

Briefly sketch the background to the current proposal, critically evaluate existing knowledge and specifically identify the gaps that the project is intended to fill.

The in vitro characterization of 3D printed PCL-TCP scaffolds has been well studied by our group. The design and laydown pattern of the scaffolds were optimized to 0/60/120° in terms of stiffness and strength⁴¹. Additionally, these scaffolds had a porosity of approximately 60%, with fully interconnected pores that facilitated cellular retention as well as media perfusion. Cell culture studies showed fibroblasts and osteoblast-like cells could proliferate, differentiate and produce cellular tissue within the scaffolds. Mechanically, PCL-TCP scaffolds were shown by our group to have improved stiffness⁴² over their PCL counterparts (Figure 3A, B) while the inclusion of TCP had also conferred bioactivity^{34,43}. On this note, we have validated the incorporation of TCP using micro-computed tomography (Figure 3C, D). The mechanical response to degradation has also been well characterized, both in vitro and in vivo^{34,37,42,44}

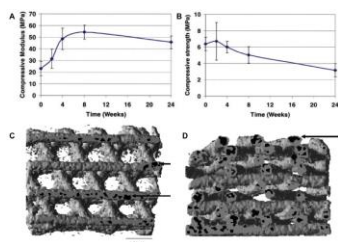


Figure 3 (A) Compressive modulus and (B) strength of PCL-TCP scaffolds, mapped over a degradation period of 24 weeks³⁷. MicroCT visualization of PCL-TCP scaffolds on their (C) top view, and (D) cross-section view. PCL struts are in grey, while TCP particles are distinctly marked in black

A. In vivo studies of PCL-TCP scaffolds in small and large animal models

Following the in vitro studies, we evaluated the biomechanical properties as well as the degradation and safety profiles of the PCL-TCP scaffolds in small animal models of rats³⁷ and rabbits^{42,45}. Importantly, these studies demonstrated that PCL-TCP scaffolds were well accepted by the hosts, without causing overt inflammatory reaction and fibrous encapsulation. Its safety was also demonstrated by evaluating host immunological response in mice⁴⁰.

Large animal studies were conducted in clinically relevant non-human primate model (*Macaca fascicularis*) for regeneration of tooth socket facial wall defects⁴⁶ as well as pig model (*Sus scrofa*) for lateral ridge augmentation⁴⁶ and mandible reconstruction⁴⁷. In the primate study, we demonstrated that PCL-TCP implants resulted in better maintenance of the alveolar contour as compared to autogenous bone grafts at 6 months (Figure 4a, b)⁴⁶. In one of the pig studies, we evaluated the use of a PCL-TCP scaffold for lateral augmentation of the alveolar ridge over a 6-month healing period (Figure 4c-f). Histological examination revealed that new bone matrix and bone marrow were **in direct contact** with the PCL-TCP scaffold rods and invading the interstices, suggesting good biocompatibility and high osteoconductivity³⁹.

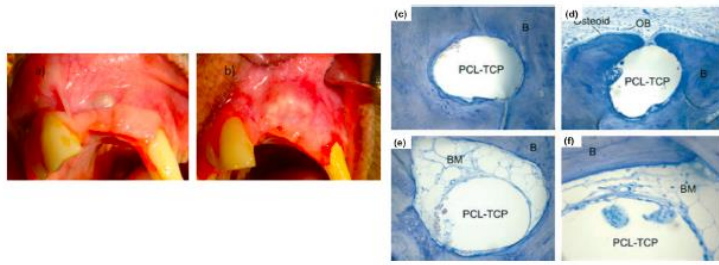


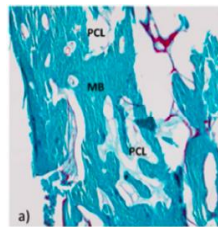
Figure 4 (a) Particulate autogenous bone and (b) PCL-TCP scaffold placed during immediate dental implant surgery. PCL-TCP scaffold group demonstrated better maintenance of the alveolar contour after 6 months⁴⁶. Histological sections of PCL-TCP showing (c) new bone matrix (B), which was directly deposited onto a rod of the scaffold. (d) Osteoid and osteoblasts (OB) were found in close proximity to a rod of the scaffold surrounded by bone matrix, B. The formation of (e) bone matrix and bone marrow (BM) were also observed at the periphery of a rod of the scaffold. Importantly, we note the (f) rare occurrence of a few multinucleated giant cells on the surface of the PCL-TCP scaffold³⁸.

B. Pilot randomized controlled clinical trial

A pilot randomized controlled clinical trial was conducted at the NDCS to evaluate the feasibility and effectiveness of using a polycaprolactone (PCL) scaffold in fresh extraction sockets for ridge preservation. The hypothesis was that the insertion of a 3D bioresorbable PCL scaffold in fresh extraction sockets allowed for normal bone healing and better maintenance of ridge dimensions after 6 months as compared to extraction sockets without the scaffold. 13 patients were recruited at the NDCS and randomized to either the test group (N =6) where a PCL scaffold was inserted in the tooth socket after extraction, or the control group (N = 7) where no space filler was used. The results showed **less vertical ridge resorption** in the test group compared to the control group and the difference was **statistically significant** in the mesio-buccal aspect (p=0.008). Micro CT and histological observations showed mainly mineralised bone formation in both groups. It was thus concluded that, within the limits of the small sample size, the insertion of a 3D bioresorbable PCL scaffold in fresh extraction sockets allowed for normal bone healing and there was better maintenance of ridge height after 6 months as compared to extraction sockets without the scaffold.³⁸ (Figure 5)



PCL scaffold was shaped to fit snugly in tooth extraction socket. The excess scaffold had been trimmed off with a scalpel.



Histology of core of bone taken 6 months after PCL scaffold insertion in tooth socket. Goldner Trichrome stain. PCL: dissolved PCL scaffold MB: mineralized bone

Figure 5: Insertion of first generation PCL scaffold in tooth extraction sockets resulted in mineralised bone formation and a lack of inflammation at 6 months³⁸.

The study which we are proposing in this grant application will be an extension of the above pilot clinical trial, except that a second generation composite polymer scaffold PCL-TCP will be used instead of the first generation PCL. We expect the results using PCL-TCP will be superior to PCL due to the improved biochemical and mechanical properties and degradation kinetics.

1.2.2 Rationale for Study Population

Justify selection of target population.

The target population are adult patients who require single tooth extraction and who are suitable for dental implant therapy after extraction. This target population has been chosen as the 3D printed investigational scaffold device is intended for use immediately following tooth extraction for alveolar ridge preservation. The preservation of the alveolar ridge dimensions will be important to create favorable conditions for subsequent dental implant placement.

1.2.3 Rationale for Study Design

This will be a prospective, open-label, randomized controlled clinical trial. As this study will compare the use of a device in a tooth socket (test group) versus no device (control group), blinding is not possible as assessors would be able to see the remnants of the scaffold in the socket during 6 months post-extraction. To reduce bias, 2 independent parties will perform the ridge dimension.

The investigator performing the Radiopacity Grading Scale will be blinded to the grouping of the radiographs. Blinding for the micro CT and histology analyses is not possible as the presence/ absence of PCL-TCP scaffold will be obvious in the specimens.

2 HYPOTHESIS AND OBJECTIVES

This study aims to evaluate the efficacy and safety of using a PCL-TCP scaffold for ridge preservation.

2.1 Hypothesis

The primary hypothesis is that the insertion of a 3D bioresorbable PCL-TCP scaffold in fresh extraction sockets allows for normal bone healing and less resorption of the alveolar ridge after 6 months compared to the resorption in extraction sockets without any space filler.

2.2 Primary Objectives

Primary aim: To evaluate if there will be less alveolar ridge resorption 6 months following tooth extraction by the insertion of a 3D printed bioresorbable PCL-TCP scaffold in the tooth socket (test group) compared to no space filler in the tooth socket (control group).

2.3 Secondary Objectives

Secondary aim 1: To compare by clinical observation and histology the healing and inflammatory response in tooth sockets of the test and control groups.

Secondary aim 2: To compare using histology and microcomputed tomography (micro CT) the quality and quantity of bone tissue formed in tooth sockets in the test and control groups after 6 months.

Secondary aim 3: To evaluate the stability of dental implants placed into healed sockets in the test and control groups using Resonance Frequency Analysis (RFA) at the time of placement (stage I implant surgery) and at 3 months post-implant insertion (stage II implant surgery).

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

There is a possibility that the jaw bone may not be preserved after tooth extraction. A bone graft may be needed to build up sufficient bone height and width for favorable implant placement. The attending surgeon will advise on the need for bone grafting and this is dependent on various factors such as the location of the jaw bone and pre-existing gum diseases. The cost of the bone graft procedure will be borne by the patient.

There is a possibility of Infection. In the event of infection, local debridement will be performed. Oral antibiotics and chlorohexidine anti-microbial mouthwash will also be prescribed. Exposed parts of the scaffold will be trimmed down. If necessary, loose scaffolds and those encapsulated in soft tissue will be removed.

2.4.2 Potential Benefits

Patients under the test group will be able to gain access to ridge preservation therapies using the novel 3D printed scaffold devices before they become widely available. The test group could potentially benefit from better ridge preservation. As part of their participation in this research study, the patients from both the test and control group will have part of their dental implant treatment cost covered.

This study will contribute to the medical knowledge about the use of the 3D printed biopolymer scaffold in ridge preservation.

3 STUDY POPULATION

3.1 List The Number and Nature of Patients to be Enrolled.

This will be a prospective, open-label, randomized controlled clinical trial in adult patients who require single tooth extraction and who are suitable for dental implant therapy after extraction. The patient will be randomised by a clinician, using sealed envelopes that has been prepared by an independent party, to either the test or control group on a 1:1 ratio:

Test Group: insertion of PCL-TCP scaffold after tooth extraction

Control Group: no space filler after tooth extraction

138 patients who give written consent to participating in the study will be recruited from the Departments of Oral & Maxillofacial Surgery and Restorative Dentistry at the NDCS. About 500 patients per year receive dental implant treatment at the NDCS. Assuming that 10% of these patients fulfil the inclusion and exclusion criteria and give consent to participating in the study, we will expect to recruit about 50 patients per year. The recruitment of 138 patients is estimated to take about 2 year and 10 months.

3.2 Criteria for Recruitment and Recruitment Process

Recruitment posters will be displayed at public locations in NDCS as well as other SingHealth hospitals, specialist centres and polyclinics. ~~The study team will also be putting up the recruitment poster on NDCS corporate social media to drive interested participants to contact NDCS or to the microsite which will be explained in details in the paragraph below.~~ All clinicians in NDCS will be informed of the study via email and their help will be sought to identify suitable patients for recruitment into the study.

Letters will be sent to private practitioners to seek for their referrals of suitable patients and the recruitment posters will also be placed at these private clinics.

An online microsite will be made available for potential/ enrolled patients to obtain more information about the study. ~~Quintiles will be using Facebook advertisements and Google Adwords to drive interested individuals to the microsite.~~ Through the microsite, potential patients can fill up an online questionnaire to screen for their eligibility. Eligible patients, who pass the online screening, will be contacted by the study coordinators to schedule for their first visit. During the first visit, the study investigators will take informed consent from the patients, screen for inclusion and exclusion criteria and enrol them into the study.

3.3 Inclusion Criteria

- Patient must be above 21 and below 60 years of age.
- Patient must be of American Society of Anesthesiologists (ASA) I or ASA II classification.
- Patient who requires single tooth extraction.
- Patient whose tooth to be extracted is bounded by adjacent teeth.
- Patient who is suitable for dental implant therapy after extraction.
- Patient with any pre-existing infection or abscess at the site of tooth extraction must be treated and resolved first prior to inclusion in the study.

3.4 Exclusion Criteria

- Patient with known allergy to biopolymer materials.
- Patient who are smokers.
- Patient who has undergone therapeutic radiation for head and neck malignant disease.
- Maxillary lateral incisor and molars; or mandibular central and lateral incisor extraction sites.
- Extraction sites with insufficient vertical bone height for implant placement without additional bone grafting (such as sinus lift procedure).

4 STUDY DESIGN

138 patients who give written consent to participating in the study will be recruited from the Departments of Oral & Maxillofacial Surgery and Restorative Dentistry at the NDCS.

Pre-extraction Preparation

Dental models and standardised dental radiographs, including periapical and orthopantomogram, will be taken. A customised acrylic dental stent will be fabricated as a reference tool for standardised measurement of ridge dimensions. Three markings will be made (mesio-buccal, mid-buccal, disto-buccal) on the acrylic stent at the intended extraction site (Figure 6)

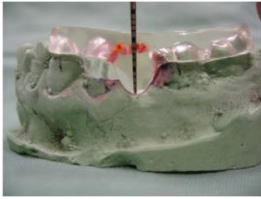


Figure 6
Surgical Extraction and Socket Management

Under local anesthesia, a trapezoidal buccal mucoperiosteal flap will be raised and an atraumatic extraction of the tooth will be performed. The tooth socket will be thoroughly debrided and any granulation tissue will be curetted out. The acrylic measuring stent will then be positioned by fitting it to the adjacent teeth and the following measurements will be taken using a periodontal probe (PCPUNC15; Hu-Friedy USA):

Ridge height

This will be measured indirectly as the vertical distance from each reference marking on the stent to the marginal bone of the tooth socket at the mesio-buccal, mid-buccal and disto-buccal aspects (Figure 1) and will be recorded as RHmeb1, RHmib1 and RHdb1 respectively.

Ridge width

This will be the horizontal distance from the buccal aspect to the lingual/ palatal aspect of the alveolar crest at the mid-buccal region of the extraction socket (RW1).

All measurements will be taken by 2 independent parties. Measurements that differ by less than or equal to 1mm will be averaged. Those that differ by more than 1mm will be repeated and a consensus will be reached by the parties. All measurements will be approximated to the nearest 0.5 mm.

The extraction sockets will be managed differently for the test and control groups:

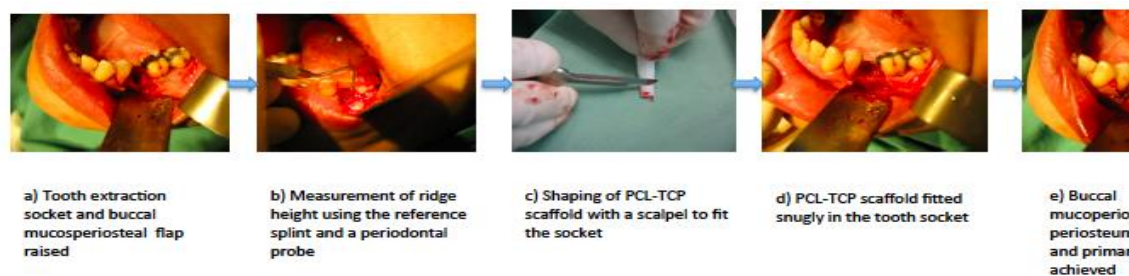
Test Group

PCL-TCP scaffold:

The PCL-TCP scaffolds will be supplied by Osteopore International (Singapore). The scaffolds will be fabricated by the latest FDM techniques (FDM 3000; Stratasys, Eden Prairie, MN), in a class 10K clean room environment. Each scaffold will have a lay-down pattern of 0°/60°/120°, porosity of 70% and will be conical in shape. The scaffolds will have a typical honeycomb structure with interconnected equilateral triangles of regular porous morphology. They will be individually packed and sterilized using gamma irradiation.

A suitable size scaffold will be chosen (small or large) based on the tooth to be extracted. During the surgery, the scaffold will be shaped by cutting and shaving with a scalpel so as to fit the extraction socket snugly at the crestal half to two-thirds aspect. A collagen membrane will be placed over the scaffold at the crestal aspect of the socket. The periosteum of the buccal flap will then be incised to allow a tension-free primary closure with 4/0 Vicryl® suture. (Figure 7)

Figure 7



Control Group

No space filler will be inserted in the extraction socket but similar to the test group, a collagen membrane will be placed over the crestal aspect of the socket and the periosteum of the buccal flap will be incised to allow a tension-free primary closure with 4/0 Vicryl® suture.

A periapical radiograph of the extraction site will be taken using standardised settings immediately postoperatively. A 5-day course of Amoxicillin (or Clindamycin if the patient is allergic to Penicillin) will be prescribed together with an analgesic and chlorhexidine digluconate 0.2% mouthrinse. The sutures will be removed 1 week postoperatively. The surgical site will be examined clinically for any signs of infection or wound dehiscence. A temporary denture will be issued where necessary. The denture overlying the extraction site will be completely relieved.

Stage I Dental Implant Surgery

Surgical placement of a dental implant will be performed at 6 months after tooth extraction. Radiographs, including a periapical of the study site, will be taken before the surgery. Following local anaesthesia and elevation of a full-thickness mucoperiosteal flap, the site will be clinically observed for any signs of inflammation, infection and presence of fibrous or bone tissue ingrowth. The same customised acrylic stent used for the case at the time of the tooth extraction will be used for measuring new ridge height dimensions in a manner similar to that described previously. Readings will be recorded as RHmeb2, RHmib2 and RHdb2. Ridge width will be measured as previously described and recorded as RW2.

The patient in either the test or control group will be taken out of the study at this stage if it is found that the extraction site has undergone extensive bone resorption such as to warrant simultaneous bone grafting with implant placement or pre-implant bone grafting with delayed implant placement.

Prior to implant placement, a core of bone of 2 mm diameter and 6 mm length at the healed extraction site will be obtained using a trephine bur (3i Implant Innovations Inc.; USA). The core of bone will be fixed and stored in 10% neutral buffered formalin and sent for microcomputed tomography (micro CT) scanning and histological preparation.

The implant site will be prepared using successive drills, according to the Straumann® (Institut Straumann AG, Basel, Switzerland) dental implant surgical protocol. A dental implant (Straumann® Bone Level) of the appropriate length and diameter will then be inserted at an insertion torque of between 20 Ncm and 40 Ncm. After placement of the dental implant, Implant Stability Quotient (ISQ) will be measured by Resonance Frequency Analysis (RFA) using the Osstell® machine. A cover screw will be placed over the implant. A releasing incision of the periosteum will be done if necessary and the surgical wound will be closed primarily with 4/0 Vicryl®.

A 5-day course of Amoxicillin (or Clindamycin if the patient was allergic to Penicillin) will be prescribed postoperatively, together with an analgesic and chlorhexidine digluconate 0.2% mouthrinse. The sutures

will be removed 1 week postoperatively. The surgical site will be examined clinically for any signs of infection or wound dehiscence. The denture overlying the extraction site will be completely relieved.

Stage II Dental Implant Surgery

This will be performed 3 months after Stage I dental implant surgery. The site will be observed for any signs of inflammation, infection as well as clinical stability of the dental implant. ISQ will be measured by RFA using the Osstell® machine before attachment of the healing abutment.

4.1 Randomisation and Blinding

Patients will be randomized after informed consent to the test or control groups at a 1:1 allocation ratio using sealed envelopes prepared by an independent statistician. Balanced intervention assignments will be achieved using permuted block randomization. Block size will be determined by the statistician responsible for generating the randomization list and will not be made known to the clinical investigator or site personnel.

Test Group: insertion of PCL-TCP scaffold after tooth extraction

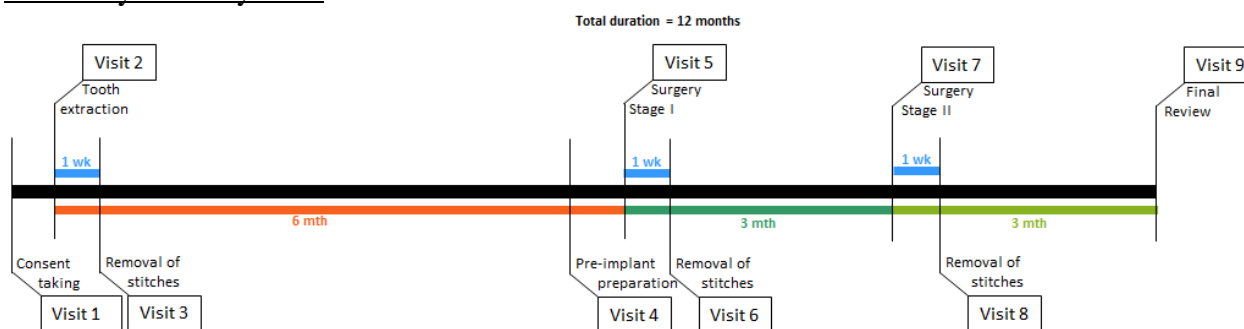
Control Group: no space filler after tooth extraction

4.2 Contraception and Pregnancy Testing

Not applicable

4.3 Study Visits and Procedures

Summary of Study Visit



Please insert visit schedule in this section.

4.3.1 Screening Visits and Procedures

Pre-screening:

Through the online microsite, potential patients will fill up an online questionnaire to screen for their eligibility of the following criteria:

- Patient must be above 21 and below 60 years of age

- Patient who requires single tooth extraction
- Patient whose tooth to be extracted is bounded by adjacent teeth
- Patient who does not have any known allergy to biopolymer materials
- Patient who does not smoke
- Patient who did not undergo any radiotherapy for head and neck cancer

Eligible patients, who pass the online screening, will be contacted by the study coordinators to schedule for their first visit.

Visit 1: Consent taking and pre-extraction preparation (Before or on the same day as Visit 2)

During the first visit, the study investigators will take informed consent from the patients, screen for the inclusion and exclusion criteria and enrol them into the study. A model of his/her teeth and a radiograph (OPG) will be taken as part of the routine care.

4.3.2 Study Visits and Procedures

Visit 2: Tooth extraction and insertion of biopolymer scaffold (if applicable, no window period)

Patient's tooth will be extracted via surgery. Local anaesthesia will be administered and part of subject's gum will be lifted to expose the tooth to be extracted. After extraction, the socket will be thoroughly cleaned and measurements of the socket will be taken.

If patients have been assigned to the test group (ie. The group that will be receiving the scaffold) a piece of the scaffold and membrane will be placed in the socket. The same area of his/her gum will be further lifted to aid in the stitching of the gum.

If patients have been assigned to the control group (ie. The group that will not be receiving the scaffold), only a membrane will be placed in the socket. The same area of his/her gum will be further lifted to aid in the stitching of the gum.

After the surgery, a periapical radiograph (estimated radiation exposure less than 0.0083 mSv) of the socket will be taken for the research purposes.

A 5-day course of medication and mouth rinse will be prescribed.

Visit 3: Removal of stitches (no window period)

This visit will be scheduled 1 week after Visit 2 or any time before Visit 4. The stitches on patient's gum will be removed and the surgical site will be examined. A temporary denture replacing the extracted tooth will be issued, if necessary.

Visit 4: Pre-implant preparation (\pm 1 month after Visit 2 or on the same day as Visit 5)

Periapical radiograph will be taken (estimated radiation exposure of less than 0.0083 mSV) for research purposes.

Another type of radiograph (OPG) and a Cone Beam CT scan will be taken as part of routine care.

Visit 5: Dental implant surgery stage I (6 months \pm 3 weeks after visit 2)

This visit will be scheduled 6 months \pm 3 weeks after Visit 2. During this visit, a dental implant will be surgically inserted. Local anaesthesia will be administered. The gum will be exposed and the bone ridge will be measured. A small part of the bone (2mm diameter by 6mm) will then be cored

from the socket. Removing (coring) a small portion of the bone is routine to an implant surgery. It will be collected for research analysis.

The dental implant will be inserted and the implant's stability (ISQ) will be measured. If needed, the gums at the implant site will be lifted to aid in the stitching of the gum.

After the surgery, a radiograph (OPG) will be taken as part of routine care.

A 5-day course of medication and mouth rinse will be prescribed.

Visit 6: Removal of stitches (no window period)

This visit will be scheduled 1 week after Visit 5. The stitches on patient's gum will be removed and the surgical site will be examined. The temporary denture will be adjusted to fit if necessary.

Visit 7: Dental implant surgery stage II (3 months \pm 3 weeks after visit 5)

This visit will be scheduled 3 months \pm 3 weeks after Visit 5. Local anaesthesia will be administered and the gums will be cut and lifted to expose the top of the dental implant. A metal cap or "healing abutment" will be inserted. The gums will then be stitched around the healing abutment.

Visit 8: Removal of stitches (no window period)

This visit will be scheduled 1 week after Visit 7. The stitches on patient's gum will be removed and the surgical site will be examined.

4.3.3 Final Study Visit:

Visit 9: Dental implant review (3 months \pm 3 weeks after visit 7)

The final visit will be scheduled 3 months after Visit 7 where the condition of the gum and implant will be reviewed and recorded.

4.3.4 Post Study Follow up and Procedures

Please refer to section 4.

4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

Patients presenting with the following will be immediately terminated from the study:

- Dehiscence defect or excessive loss or fracture of the buccal bony socket wall (> 20% loss) noted immediately after tooth extraction
- Extensive bone resorption of the alveolar ridge noted before Stage I Implant Surgery such as to warrant bone grafting procedures before dental implant placement
- Serious infection or any adverse reaction to the PCL-TCP scaffold noted at anytime during the treatment period

4.4.2 Discontinuation Visit and Procedures

Voluntary withdrawal from study:

Patients who have not received the test material i.e. PCL-TCP scaffold, shall be offered the appropriate standard of care management for tooth loss.

Patients who have received the PCL-TCP scaffold shall be evaluated 3 months after the date of withdrawal for the condition of the gum, particularly any signs of infection or dehiscence and managed accordingly. In the absence of any complications, the patient shall be offered the appropriate standard of care management for tooth loss.

5 TRIAL MATERIALS

5.1 Trial Product (s)

Test Group

PCL-TCP scaffold:

The PCL-TCP scaffolds will be supplied by Osteopore International (Singapore). The scaffolds will be fabricated by the latest FDM techniques (FDM 3000; Stratasys, Eden Prairie, MN), in a class 10K clean room environment. Each scaffold will have a lay-down pattern of 0°/60°/120°, porosity of 70% and will be conical in shape. The scaffolds will have a typical honeycomb structure with interconnected equilateral triangles of regular porous morphology. They will be individually packed and sterilized using gamma irradiation.

A suitable size scaffold will be chosen (small or large) based on the tooth to be extracted. During the surgery, the scaffold will be shaped by cutting and shaving with a scalpel so as to fit the extraction socket snugly at the crestal half to two-thirds aspect. A collagen membrane will be placed over the scaffold at the crestal aspect of the socket. The periosteum of the buccal flap will then be incised to allow a tension-free primary closure with 4/0 Vicryl® suture.

Control Group

No space filler will be inserted in the extraction socket but similar to the test group, a collagen membrane will be placed over the crestal aspect of the socket and the periosteum of the buccal flap will be incised to allow a tension-free primary closure with 4/0 Vicryl® suture.

5.2 Storage and Drug Accountability

The PCL-TCP scaffold will be stored between -10 and 25 degrees Celsius (both temperature inclusive).

6 TREATMENT

6.1 Rationale for Selection of Dose

Not applicable

6.2 Study Drug Formulations

Not applicable

6.3 Study Drug Administration

Not applicable

6.4 Specific Restrictions / Requirements

Not applicable

6.5 Blinding

As this study will compare the use of a device in a tooth socket (test group) versus no device (control group), blinding is not possible. To reduce bias, 2 independent investigators will perform the ridge dimension. The investigator performing the Radiopacity Grading Scale will be blinded to the grouping of the radiographs.

Blinding for the micro CT and histology analyses is not possible as the presence/ absence of PCL-TCP scaffold will be obvious in the specimens.

6.6 Concomitant therapy

On visit 2 and 5, a 5-day course of Amoxicillin (or Clindamycin if the patient was allergic to Penicillin) will be prescribed postoperatively, together with an analgesic and chlorhexidine digluconate 0.2% mouthrinse.

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that:

- results in or contributes to death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

7.2 Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

Reporting of adverse events involves the PI submitting to the approving CIRB the completed SAE Reporting Form within the stipulated timeframe. PI is responsible for informing the institution representative (local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- SAE that result in death, regardless of causality, should be reported immediately - within 24 hours of the PI becoming aware of the event.
- Local life-threatening (unexpected/ expected) SAE should be reported no later than 7 calendar days after the Investigator is aware of the event, followed by a complete report within 8 additional calendar days.
- Local unexpected SAE that are related events, but not life-threatening, should be reported no later than 15 calendar days after the investigator is aware of the event.
- An increase in the rate of occurrence of local expected SAE, which is judged to be clinically important, should be reported within 15 calendar days after the PI is aware of the event.
- Local expected SAE should be reported annually (together with Study Status Report for annual review).
- Local unexpected and unlikely related SAE that are not life-threatening should also be reported annually (together with Study Status Report for annual review).
- Local unexpected AE that are related events should be reported at least annually (together with Study Status Report for annual review).

- Non-local unexpected SAE that are fatal or life threatening and definitely/probably/possibly related should be reported not later than 30 calendar days after the PI is aware of the event.

7.3 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 will be reported to HSA. All SAEs will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-up 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.

7.4 Safety Monitoring Plan

At each visit, the attending clinician(s) will review the patients' condition for any complication and other safety concerns, both related and/or unrelated to the trial. Appropriate clinical advice will be provided to manage the condition. Conditions requiring discontinuation/ withdrawal will be handled as described in Section 4.4.

In the case of any injuries during the course of this study, patients may contact the Principal Investigator and/or the study team at the telephone numbers indicated in the patient information sheet. Appropriate clinical advice will be given to manage the condition.

Please refer to Section 8.1 for the data quality assurance.

7.5 Complaint Handling

Complaints will be handled by the study coordinator, co-investigators and/or principal investigators. If required, an investigation will be conducted by the NDCS research committee, and corrective and preventive action plans will be implemented following the committee's recommendation.

8 DATA ANALYSIS

8.1 Data Quality Assurance

The source document will be recorded and signed off by the appropriate study team member(s) obtaining

the respective measurements. The principal investigator will verify and counter-sign on the source document to ensure that all the appropriate data has been collected. The recorded clinical trial data in the source document will then be entered into an online database by the study coordinators. The principal investigator will verify and endorse on the system that the data has been entered correctly.

The sponsor and/or the appointed study monitor will also audit the source document and online database, and if required, recommend corrective and preventive action plans to ensure data integrity.

8.2 Data Entry and Storage

Source data will be keyed into the eCRF (Oracle system) directly. The access to the source documents will be granted to the study coordinators, study team members, sponsors, monitors and/or relevant regulatory authorities.

Secured access to the electronic database, via individual password-protected login accounts, will be granted to the study coordinators, study team members, sponsors, monitors and/or relevant regulatory authorities as required.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

The sample size is calculated based on comparison of mean change in aggregate ridge height (mean of mesio-buccal, mid-buccal, and disto-buccal ridge heights) at 6-months post extraction between the test (PCL-TCP scaffold) and control (no space filler) groups. A sample size of 138 patients (69 per group) will be required to detect a difference of 0.5 SD in mean change in aggregate ridge height between the test and control groups to achieve 80% power at 5% (two-sided) level of significance, and considering 7% drop-out rate.

9.2 Statistical and Analytical Plans

The study will have no interim analysis. A detailed statistical analysis plan for the final analysis will be prepared before the database lock. Briefly, the primary outcome – aggregate change in ridge heights at 6-months post-extraction will be compared between the test and control groups using the two-independent samples t-test. Secondary outcomes - change in individual ridge heights, ridge width, Radiopacity Grading Scale, BV%, and ISQ will be also analysed similar to the primary outcome.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Data will be evaluated for adherence with the protocol and for accuracy in relation to source documents by SCRI. Please refer to monitoring plan for scope of monitoring.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final study protocol, including the final version of the Patient Information and Informed Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

Patient will be given time to consider whether or not he/she wants to participate in the project. The patient may then bring the PIS home and the consent will be taken at the next visit. However, if the patient is able to decide to participate at the first visit, consent will be taken at the first visit. Consent will be taken in NDCS outpatient clinic. The place is chosen as it is an enclosed area where the PI is able to explain the study and answer patient's queries clearly.

12.2 Confidentiality of Data and Patient Records

Research data will be stored in a password protected computer located in the research office. Hard copies of the research documents / data collection forms will be stored in locked cabinets in the research office.

Only the study team members will have access to the research data, stored as a registry of patients with case number and a study database using only patient case numbers with no other patient identifiers.

13 PUBLICATIONS

Please refer to the publication policy adapted from the International Committee of Medical Journal Editors.

<http://www.icmje.org/recommendations/browse/roles-and-responsibilities/>

14 RETENTION OF TRIAL DOCUMENTS

Essential documents will be retained until at least 2-years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

The sponsor will inform the investigator(s)/institution(s) in writing of the need for record retention and will notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

15 FUNDING and INSURANCE

This clinical trial study is supported by NMRC Clinical Trial Grant Co-Development Scheme (CTG-CO-D) and contributions from both NDCS and Osteopore International (Singapore). Clinical trial insurance coverage is obtained by Osteopore International (Singapore). For details, please refer to the signed research collaboration agreement (dated 24 December 2014) and addendum (dated 22 December 2017).