

Instructions: The purpose of this research protocol is to provide IRB members and reviewers with sufficient information to conduct a substantive review. If a separate sponsor’s protocol exists, submit it in addition to this document.

Complete all of the sections below. For more detailed instructions, consult the Investigator’s Manual or IRB website (links provided below).

GENERAL INFORMATION	
Protocol # (if assigned): IRB15-3772	
Version Date: 5/6/2016	Version Number: 1.7
Principal Investigator: Eli Machtei DMD	
Faculty Advisor (if PI is a student): N/A	
Protocol Title: Dimensional changes of the keratinized gingiva and vestibular depth following socket preservation procedure using two surgical protocols	

1. Specific Aims

The primary objective of this study is to assess two widely accepted surgical protocols (both used interchangeably as standard of care) that are used to maintain hard and soft tissue after a tooth extraction.

It is currently unclear if one treatment is more effective than the other. The two treatments being compared are:

Treatment 1: A cross-linked membrane is used in secondary intention healing.

Treatment 2: A non-cross-linked membrane is used in primary intentional healing.

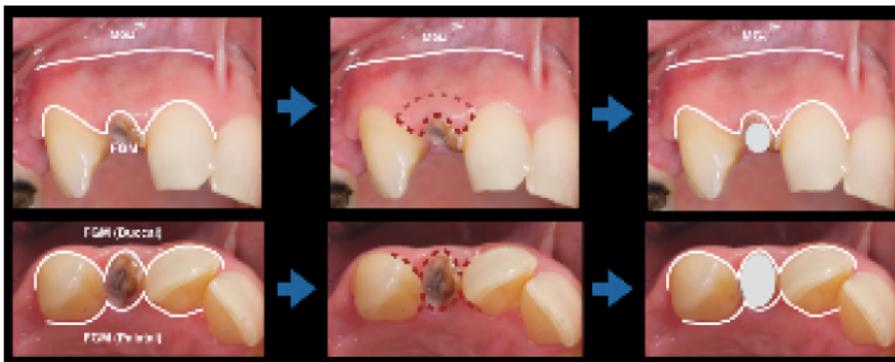
Non-Crosslinked Membrane: A collagen covering used to keep bacteria out, hold the bone graft in place, and to separate the gum and bone during healing.

Crosslinked Membrane: A stronger more long lasting collagen covering which functions similarly to the non-crosslinked membrane described above.

Primary intention healing (submerged healing): The wound edges are brought together and closed (ie papercut).

Secondary intention healing (non-submerged healing): The wound edges are not brought together (ie knee scrape).

Treatment 1



Treatment 2



2. Background

2.1 Provide the scientific background and rationale for the study

HARD TISSUE DIMENSIONAL CHANGES

Socket preservation procedures have been developed with the aim of avoiding or reducing dimensional shrinkage of alveolar bone after tooth extraction which in turn will facilitate subsequent prosthetic treatment using dental implants or fixed partial denture. Both preclinical and clinical studies have investigated the changes which occur after tooth extraction when the site is left to heal on its own and when socket preservation procedures have been performed.

Preclinical Studies

Cardaropoli et al. 2003 ¹ utilized the canine model to study hard tissue remodeling after tooth extraction and demonstrated that the socket is initially occupied by a coagulum which is then sequentially replaced by provisional connective tissue matrix, woven bone and lamellar bone.

During remodeling, the hard tissue undergoes dynamic changes which include a crestal height reduction of the buccal and lingual walls (greater on the buccal wall) and alveolar width resorption from the surfaces of the outer buccal and lingual walls (Araujo et al. 2005) ².

Fickl et al. 2008 ³ compared post extraction resorption rates after socket preservation to untreated controls in canines. All treatment groups displayed contour shrinkage of the buccal plate but socket preservation was able to limit hard tissue alterations. Utilizing a xenograft, Araujo et al. 2009 ⁴, found that the percent change in surface area of the marginal portion of the extraction site was -35% in the negative control group and -12% in the grafted group. The placement of bone graft into an extraction socket counteracted the marginal ridge reduction by serving as a scaffold for modified tissue modeling.

Conversely, other canine studies were unable to find significant merit in the use of socket preservation procedures. Rothamel et al. 2008 ⁵ examined the use of a nano crystalline hydroxyapatite paste on dimensional ridge alterations and found no statistically significant difference between the test and control groups. Araujo et al. 2011 ⁶ compared the use of autologous bone with inorganic bovine bone and demonstrated that autologous bone did little to prevent hard tissue contraction (-25%) while bovine derived graft material showed a +3.6% change with delayed hard tissue healing. The -25% change (Araujo et al. 2011) ⁶ was similar to the -30% ridge reduction found in non-grafted sites in a previous study (Araujo et al. 2005) ⁷.

Araujo et al. 2005 noted that in addition to internal resorption of the extraction site, external resorption occurred from the outer surfaces of the buccal and lingual walls. Fickl et al 2008 ⁸ examined external boney resorption associated with surgical trauma. The combined internal and external osteoclastic resorption resulted in

significantly greater hard tissue shrinkage. Thus, avoiding muco-periosteal flap elevation and allowing healing by secondary intention can minimize crestal bone loss.

Clinical Studies

Considering the variations within individuals and differences in anatomic sites, a considerable 11-22% of alveolar height loss and a 29-63% decrease in alveolar width were reported during the first 6 months after extraction when the site is allowed to heal un-assisted (Tan et al. 2012)⁹. When socket preservation therapies were applied to extraction sites, they demonstrated statistically significant reduction of post-extraction dimensional changes. Vignoletti et al. in 2012¹⁰ found a 1.83mm decrease in resorption of the alveolar ridge width and 1.47mm decrease in alveolar height resorption. Meta-analysis by Avila-Ortiz et al. 2014¹¹ revealed a similar picture: ridge resorption in the socket preservation group was 1.89 mm less than in the control group. Also, less vertical resorption was found at the midbuccal (2.07mm), midlingual (1.18mm), medial (0.48mm), and distal (0.24mm) aspects. Willenbacher et al. 2015¹² found that 1.31-1.54mm of alveolar width and 0.91-1.12mm of bone height could be preserved with socket preservation therapy.

SOFT TISSUE DIMENSIONAL CHANGES

Untreated extraction sites have exhibited soft tissue thickness increase of 0.4-0.5mm (Iasella et al. 2003¹³) and keratinized tissue width increase of 0.7mm (Barone et al. 2014¹⁴). When indicated, the maintenance of hard and soft tissue at the newly edentulous site can preserve the contours and structure of existing bony walls, reduce the need for future augmentation procedures, and improve the final esthetic results.

In comparison to sites that healed unassisted, those that had undergone ridge preservation surgery exhibited changes in gingival thickness, width and vestibular depth. Gingival thickness differences between test group and untreated control were only statistically significant in buccal sites (Vignoletti et al. 2011¹⁰). Gingival width has been found to have a larger coronal shift of 1.1mm after socket preservation when compared to 0.7mm in unassisted healing (Barone et al. 2014¹⁴). In a study of the long-term stability of soft tissue after socket preservation, Rocuzzo et al. 2014¹⁵ found that with maintenance, the risk of soft tissue recession around implants is less than 1.0mm after 10 years.

Vestibular Depth Dimensional Changes

Alveolar bone resorption often in combination with coronally repositioned flaps can contribute to a reduction in vestibular depth. Halperin-Sternfeld et al. (in press)¹⁶ have found that shallow vestibules (<4mm) were associated with increased recession, relative attachment level, and bleeding on probing as well as decreased keratinized tissue width around implants. The effect of socket preservation upon vestibular depth has seldom been studied, but its effect on keratinized tissue and vestibular depth can be important in esthetics, hygiene maintenance, and functionality of the final prosthesis.

SURGICAL TECHNIQUES AND MATERIALS

A number of surgical techniques can be utilized to preserve soft and hard tissues post-extraction. These include: (1) flapped or flapless access, (2) primary or secondary intention wound healing and, (3) graft material, membrane barrier, or a combination of both. When compared to a flapless surgical approach, full thickness flap reflection has a disruptive effect on the osteogenic potential of the periosteum (Araujo et al. 2005⁷). However a flapped surgical procedure has greater potential for achieving primary wound closure; an important technique for preventing bacterial invasion of the socket that has been shown to reduce the horizontal bone changes (Vignoletti et al. 2011¹⁰). In all cases, an atraumatic extraction, whenever possible, is an essential part of the protocol.

THE ROLE OF MEMBRANE BARRIERS IN SOCKET PRESERVATION

Barrier membranes facilitate cell exclusion, maintain the space and stabilize the graft and blood clot in socket preservation; therefore, their biodegradability during healing is crucial (Tal et al. 2008¹⁷). Among the surgical techniques regarding barriers are the use of membranes alone or in conjunction with bone grafting. Meta-analysis by Oregas et al. 2013¹⁸ found that the use of barrier membranes alone can improve normal wound healing after extraction. Vignoletti et al. 2012¹⁰ found that the use of barrier membranes with or without bone graft reduced horizontal bone resorption.

Non-resorbable barriers such as expanded polytetrafluoroethylene (ePTFE) membranes require a surgical reentry for membrane retrieval and, if exposed to the oral environment, become colonized with bacteria thus requiring early removal with considerable diminished bone formation (Machtei 2001¹⁹). In contrast to ePTFE membranes, bioabsorbable barriers obviate the need for a re-entry to remove the membrane and if exposed, are less likely to become infected. When exposed, both cross-linked and non-crosslinked membranes are degraded by bacterial collagenolytic enzymes which can result in some bone graft resorption (Moses et al 2005²⁰). Kodama et al. 1989²¹ have found a negative correlation between the degree of collagen cross-linking and membrane resorption rate. Several different techniques for achieving collagen cross-linking involve ultraviolet light radiation, glutaraldehyde, imides or ribose (Tal et al 2006¹⁷). Ribose sugar mediated cross-linking shows prolonged barrier functionality, no adverse tissue reactions, and can enable high degrees of cross-linking (Friedmann et al 2002²²).

Cross-linked membranes have the advantage of greater structural integrity which enable 4-6 months of functionality compared to 4-6 weeks from a non-cross-linked membrane (Moses et al. 2005²⁰, Zitzmann et al. 1997²³). Moses et al. 2005²⁰ found that while cross-linked and non-cross-linked membranes have the same exposure rate, 69% of cross-linked collagen barriers had soft tissue healing over exposures when compared to 12% of non-cross-linked collagen barriers.

2.2 Describe the significance of the research, and how it will add to existing knowledge

If Treatment 1 proves to have significantly better soft and hard tissue outcomes, it could become the new standard of care. Even if both treatments have similar outcomes, then the simplicity of the surgical technique of Treatment 1 might become the new preferred standard of care resulting in simpler and less traumatic surgical procedures.

3. Study Setting

1. Identify the sites or locations where the research will be conducted.

This study will be conducted at the Harvard School of Dental Medicine located at 188 Longwood Ave., Boston, MA 02115.

2. Describe the Principal Investigator's experience conducting research at study site(s) and familiarity with local culture

The PI, Eli Machtei DMD, is a seasoned periodontist with years of experience with regenerative techniques such as the one being employed in this study.

3. Is the research conducted outside the United States?

No Yes: If yes; describe site-specific regulations or customs affecting the research, local scientific and ethical review structure

No

3.4. Are there any permissions that have been or will be obtained from cooperating institutions, community leaders, or individuals, including approval of an IRB or research ethics committee?

No Yes: If yes; provide a list of the permissions (also include copies with the application, if available)

Yes: IRB

4. Study Design

1. Describe the study design type

The present study will be a prospective, parallel-arm, human, randomized clinical study. Participants who are screened and accepted into the study will be randomized into Treatment 1 and Treatment 2 groups using a web-based randomization tool: randomizer.org.

2. Indicate the study's duration - and the estimated date of study completion

Individual participants are anticipated to be involved in the study for 5 months. The study's overall anticipated duration is 18 months with an estimated completion date: May 2017.

3. Indicate the total number of participants (if applicable, distinguish between the number of participants who are expected to be screened and enrolled, and the number of enrolled participants needed)

In the present study, no more than 60 participants are expected to be screened and no more than 30 participants will be enrolled. This allows for a 15% withdrawal rate which will not require supplemental recruitment. If more than 15% withdraw, then supplemental recruitment will be initiated after approval of an increase in the enrollment number from the IRB via modification.

4. List inclusion criteria

- Within the age range of 20-80 years old.
- Healthy (ASA I or ASA II) with no conditions which alter wound healing.
- Has a tooth requiring extraction with two neighboring teeth on either side of it and intact bony walls.
- Willing to participate in the study and sign the informed consent.
- Patient intends to have an implant to replace the tooth.

5. List exclusion criteria

- Outside of the range of 20-80 years old.
- The patient has systemic conditions that could alter wound healing.
- Patient does not wish for the extraction site to be reentered surgically (i.e. no intention to get an implant)
- Based on visual examination the patient has:
 - Tooth anatomy requiring aggressive bone removal or flap reflection as part of its extraction.
 - Severe local infection at the extraction site.
 - Tooth exhibiting resorption of buccal or lingual plates.
 - Absence of keratinized tissue buccal to the tooth to be extracted.
 - Reduced vestibular depth ≤ 3 mm buccal to the tooth to be extracted.

6. Describe study procedures

Study Procedures

Screening	<p>Patients seen in the Harvard Dental Center pre-doctoral and resident clinics will be approached to gauge their interest in participating in the study. Patients will be informed of the general aim of the study, the overall cost, materials, procedure, and timeline of their involvement. Interested patients will be screened for eligibility by visual inspection of their tooth. If the patient agrees to participate, informed consent will be obtained. If the patient would like time to decide on his/her participation, they will be given a copy of the informed consent to take home. Patients that do not yet sign the informed consent at this visit will do so at Visit #1.</p>
Visit #1	<ul style="list-style-type: none"> • Dental CT Scan: This is an additional scan that is not commonly done in private practice but can be standard of care at HSDM depending on the specific case. This scan will be required for participation in this study.
Visit #2	<p>Patients will be randomized into Treatment 1 or Treatment 2 using randomizer.org. Prior to the surgery measurements will be taken:</p> <ul style="list-style-type: none"> • Pre-Operative measurements will be taken of teeth, gums and bone before tooth extraction after the patient has been numbed. <ul style="list-style-type: none"> • Gums will be measured by placing a periodontal probe (a small ruler) on top of the tissue. • Gum thickness will be measured with a thin needle and rubber stopper. • Intra-operative dimensional measurements will be taken during tooth extraction. The patient will still be numb. <ul style="list-style-type: none"> • Bone width will be measured with a caliper (an instrument that gently goes around the bone). • Teeth and bone will be measured by placing a periodontal probe (small ruler) on top of the structures.
Visit #4	<p>Six week post-operative follow-up. Will examine site for treatment side effects including intra-oral findings and patient report. No measurements will be taken; only visual inspection to ensure normal healing.</p>
Visit #5	<p>At the time of implant placement (by the patient's own dentist) as per the standard of care, the study team will only be involved in the collection of the following data:</p> <ul style="list-style-type: none"> • Dental impressions will be taken. • Pre-Operative and Intra-operative measurements will be repeated.

Standard of Care Procedures (for Information Purposes)

Visit #1	<p>Patients will sign the treatment informed consent, receive oral hygiene instruction, Baseline data will be obtained (unless already on file in the dental record).</p> <ul style="list-style-type: none"> • Full mouth X-Ray series • Intra-oral photo series • Dental impression (to be turned into stone cast) <p>Patients will then be scheduled for the next visit.</p>
Visit #2	<p>Surgical Treatment (One treatment option would be chosen and performed)</p> <p>Treatment 1</p> <ul style="list-style-type: none"> • Atraumatic extraction (without gum repositioning aka “flap elevation”). • Freeze-Dried Bone Allograft (RegenerOss®) placed. • Crosslinked collagen membrane (OssixPlus®) placed. • Secondary closure (with sutures). <p>Treatment 2</p> <ul style="list-style-type: none"> • Atraumatic extraction (with gum repositioning aka “full thickness flap elevation”). • Full thickness flap elevation. • Freeze-Dried Bone Allograft (RegenerOss®) placed. • Non-crosslinked collagen membrane (Bio-Gide®) placed. • Primary closure (with sutures). <p>All patients will be given post-operative instructions in written and verbal forms.</p>
Visit #3	<p>Two week suture removal and post-operative follow up. Will examine site for treatment side effects including intra-oral findings and patient report. No measurements will be taken; only visual inspection to ensure normal healing.</p>
Visit #5	<p>Four month post-operative implant placement performed by the patient’s own dentist not the study staff.</p> <ul style="list-style-type: none"> • Peri-apical radiographs will be taken. • CT scan will be taken.

7. Does the study involve the collection of data/specimens (including the use of existing data/specimens)?

No Yes: If yes; indicate how, when, where and from whom specimens or data will be obtained

Yes: Data in the form of clinical measurements, radiographs and CT scans will be collected directly from participants. All data will be collected at baseline and again at 4 months post operatively as per standard of care. If there are existing radiographs in the patient’s dental record, they will not be repeated at Visit #1 and that existing data will be used in the study

8. Is there a data and safety monitoring plan (required for greater than minimal risk studies)?

No Yes: If yes; describe the plan

Yes: To determine that participants remain safe during the study, each visit will include an examination of possible treatment side effects including both intra-oral findings and patient reports. Treatment side effects would all be expected side effects of the standard of care and can include infections during healing, difficulty in wound clotting, discomfort during healing or swelling or bruising after surgery. There are no specific risks concerning the non-standard of care research components of the study (ie Pre-Operative and Intra-operative measurements, six week follow-up exam). Safety information will be collected on case report forms (CRF) at each study visit. If serious severe adverse events (SAE) occur (i.e. infection, excessive bleeding or allergic reaction), then the study will recall all patients within the same treatment protocol for thorough examination for any potential adverse effects. Potential SAE will be found via patient report and visual inspection during follow-up exams. All treatment materials that will be utilized in the present study are FDA approved; the likelihood of an SAE arising from this treatment are slim.

9. Are there any anticipated circumstances under which participants will be withdrawn from the research without their consent?

No Yes: If yes; describe the circumstances as well any associated procedures to ensure orderly termination

Yes: Conditions that will require patient removal include failure to show up for study visits, changes in medical condition that might alter wound healing, or severe abscess in the surgical site. The patient would then be referred for continued care to their existing dentist (who would be located in the same clinic for a seamless transition).

5. Data/Statistical Analyses Plan

1. Briefly describe the plan for data analysis (including the statistical method if applicable)

Statistical analysis: Descriptive analysis will be performed on the differences in primary (gingival width) and secondary (vestibular depth, gingival thickness, radiographic and clinical alveolar height, alveolar width) outcome variables all of which will be measured in millimeters on a continuous scale. Two sample t-tests for independence samples will be used to compare mean values between treatment groups to evaluate statistical significance. A standard significance level of 0.05 will be chosen determined significance. All statistical analysis will be performed using STATA software version 12.

2. Is there a sample size/power calculation?

No Yes: If yes; describe the calculation and the scientific rationale, and, if applicable, by site and key characteristics such as participant demographics

Using a power of 90%, alpha of 0.05 with mean intergroup difference of 1.0mm a sample of 15 in each group will be required.

6. Recruitment Methods

1. Does the study involve the recruitment of participants?

No: If no, skip to 7.1

Yes: If yes; indicate how, when, where, and by whom participants will be recruited

Patients who are currently in treatment with Harvard School of Dental Medicine pre-doctoral and resident clinics will be initially invited to join the study by research staff, whom are not their treating dentist. If their dentist is a member of this research project, a different study staff member will recruit, consent, and enroll the participant. As per the culture of an academic dental setting, attendings routinely check on students' progress. As the study staff encounters cases that seem to meet the study inclusion criteria (i.e., need a tooth removed and intend to get an implant) during these checks, they will approach those patients as appropriate for the study. Those who qualify to participate (via a visual exam based on the Eligibility Checklist) and who might wish to enter the study will be provided with information about the nature of the study, any potential side effects and alternative treatment options. This will be provided in the form of oral conversation referring to the consent form which they will be allowed to take home for their information. All recruitment activities will occur at a private dental chair at the time of their dental visit.

2. Are there any materials that will be used to recruit participants, e.g., emails, posters, and scripts?

No Yes: If yes; provide a list of the materials (also include copies with the application)

Yes: Recruitment Script

7. Available Resources

1. Describe the feasibility of recruiting the required number of participants within the recruitment period

Due to the relative frequency of patients seeking dental treatment at the HSDM Periodontology division who require tooth extraction as part of their therapies, recruiting the expected number of participants is feasible within the timeline that we have highlighted above (12 months).

2. Describe how the Principal Investigator will ensure that a sufficient amount of time will be devoted to conducting and completing the research.

The PI will dedicate 50% of his clinical time for the study. The Co-PI will compliment this. The investigator will be dedicated to patient recruitment and monitoring thought the study.

3. Are there research staff members, in addition to the Principal Investigator?

No: If no, skip to 7.5

Yes: If yes; outline training plans to ensure that research staff members are adequately informed about the protocol and study-related duties

Yes: The Co-Investigator, David Kim DMD, is a seasoned periodontist with years of experience with regenerative techniques such as the one being employed in this study. Other study team members, Heather Wong DDS and Chia-Yu Chen DDS, are both graduate students in the department of Periodontology at HSDM. All research staff members will be adequately informed about the protocol and study-related duties. All research staff members will be able to obtain informed consent. The PI and Co- PI will be performing the surgery.

4. Describe the minimum qualifications for each research role (e.g., RN, social worker) their experience in conducting research, and their knowledge of local study sites and culture

To be on the research team, one needs to have DMD/DDS license.

5. Briefly describe how the research facilities and equipment at the research site(s) support the protocol's aims, e.g., private rooms available for interviews, etc.

The Periodontology clinic at the Harvard School of Dental Medicine is equipped with dental chairs, surgical materials, and surgical instrumentation which support periodontal surgical procedures and exams.

6. Are there provisions for medical and/or psychological support resources (e.g., in the event of incidental findings, research-related stress)?

No Yes: If yes; describe the provisions and their availability

No

8. Vulnerable Populations

1. Are there any potentially vulnerable populations (e.g., children, pregnant women, human fetuses, neonates, prisoners, elderly, economically disadvantaged, employees or students of the investigator or sponsor, undocumented, terminally ill, cognitively impaired or mentally ill, etc.)?

No: If no, skip to 9.1

Yes: If yes; identify all vulnerable populations

No

2. Describe safeguards to protect their rights and welfare

N/A

9. Consent Process

1. Will consent to participate be obtained?

No: If no, skip to 9.5

Yes: If yes; describe the setting, role of individuals involved, timeframe(s), and steps to minimize coercion/undue influence during the consent process (at the time of initial consent and throughout the study)

Yes: Participants will be initially invited to join the study by the research staff who will provide them with information about the nature of the study, any potential side effects, and alternative treatments. This will be done in the form of oral conversation and further elaborated in a written consent form. Participants will be able to take a copy of the consent form home.

2. Are there any special populations?

No Yes: If yes; describe the process to obtain consent, permission or assent

No

3. Will consent of the participants be documented in writing?

Yes No: If no; describe the rationale for requesting a waiver or alteration of documentation of consent (and/or parental permission)

Yes

4. **Will participants be provided with a copy of their signed consent form or information sheet (when a consent form is not signed)?**

Yes No: If no; explain any extenuating circumstances that make it impossible or inappropriate to meet this requirement, ie, doing so may place participants at increased risk, if inadvertently disclosed

Yes

5. **Is a waiver or alteration of consent (and/or parental permission) being requested?**

No Yes: If yes; describe the rationale for the request. If the alteration is because of deception or incomplete disclosure, explain whether and how participants will be debriefed (include any debriefing materials with the application)

No

10. Risks

1. **Are there any reasonably foreseeable risks, discomforts, and inconveniences to participants and/or groups/communities?**

No Yes: If yes; indicate probability, magnitude, and duration of each (note that risks may be physical, psychological, social, legal, and/or economic)

Yes, the list of side effects below associated with any oral surgical procedure is to be expected; however, the treatments are Standard of Care, as are the risks:

- Swelling of face and gums
- Bruising of skin at the area of tooth removal
- Discomfort at the surgery site
- Minor bleeding from the tooth removal site
- During tooth extraction, infection, communication with sinuses (upper teeth) and nerve injury (lower teeth) are rare occurrences that pose a minimal risk of surgery.

Inconveniences that are specific to research activities include:

- Probe measurements may produce minimal discomfort as a small ruler is placed into gum pockets.
- Dental impressions can be slightly but temporarily uncomfortable.
- The time required to attend the six week post-operative visit.
- Due to the collection of identifiable data, a breach in confidentiality is a possible but minimal risk.
- An additional CT scan is also a foreseeable inconvenience but has benefits to enable better understanding of the nature of the healed site to much better plan the future implant. As with all CT scans, minimal radiation is produced. This additional scan is not commonly done in private practice but can be standard of care at HSDM depending on the specific case. This scan will be required for participation in this study.

2. **Identify whether any of the information collected, if it were to be disclosed outside of the research, could reasonably place the participant at risk of criminal or civil liability or be damaging to the participant's financial standing, employability or reputation.**

The collection of medical information could potentially cause embarrassment (i.e. the knowledge of tooth extraction, implant placement).

3. **Outline provisions in place to minimize risk**

To minimize risk, all standard of care procedures will be carried out according to the standard operating procedure for tooth extraction and socket preservation. All the surgical procedure will be performed by the PI or the Co-PI both very experienced in these procedures.

Non standard of care procedures will carefully monitored to reduce risk as follows:

- Probe discomfort will be managed with gentle patient interactions and open communication.

- Dental impression will be done in an efficient and gentle manner.
- Breaches of confidentiality will be avoided by keeping all medical and patient related information in a locked cabinet within a locked room. No medical record numbers will be recorded. All radiographs will be taken with lead aprons utilizing the radiation safety principle: ALARA (as low as reasonably achievable).

11. Benefits

1. Describe potential benefits of study participation (indicate if there is no direct benefit)

Study participants are likely to benefit from this study regardless of the group that they will be assigned to as both modalities are likely to yield positive and significant results and would have been done regardless of the research study as a part of improving their dental health.

2. Describe potential benefits of the research to the local community and/or society

If Treatment 1 proves to have significantly better soft and hard tissue outcomes, it could become the new standard of care. Even if both treatments have similar outcomes, then the simplicity of the surgical technique of Treatment 1 might become the new preferred standard of care resulting in simpler and less traumatic surgical procedures.

12. Reportable Events

1. Outline plans for communicating reportable events (e.g., adverse events, unanticipated problems involving risks to participants or others, breach of confidentiality)

Reportable events will be reported to the IRB in accordance with IRB policies within 5 business days from the time the study team becomes aware of the information. Reportable events will also be communicated to the sponsor within the same time frame.

13. Research Related Injuries (this section must be completed for any greater than minimal risk research)

13.1 Are there provisions for medical care and compensation for research-related injuries?

No Yes: If yes; outline these provisions (Please note that although Harvard's policy is not to provide compensation for physical injuries that result from study participation, medical treatment should be available including first aid, emergency treatment and follow-up care as needed. If the research plan deviates from this policy, provide appropriate justification.)

If physical injury resulting from participation in this research should occur, although Harvard's policy is not to provide compensation, medical treatment will be available including first aid, emergency treatment and follow-up care as needed, and your insurance carrier may be billed for the cost of such treatment. In making such medical treatment available, or providing it, the persons conducting this research project are not admitting that your injury was their fault.

14. Participant Privacy

1. Describe provisions to protect participants' privacy (their desire to control access of others to themselves, e.g., the use of a private interview room) and to minimize any sense of intrusiveness that may be caused by study questions or procedures

Patient's private information will be obtained in a private environment (private dental chair) and recorded in the CRF that is not available to anyone outside of the study investigators. Surgeries and follow up visits will be performed within the same private dental environment where patients generally receive care.

15. Data Confidentiality

1. Will the information that is obtained be recorded in such a manner that participants can be identified, directly or through identifiers linked to the participants?

No: If no, skip to 16.1

Yes: If yes; either state that participants will be told that their data will be public or describe provisions to maintain the confidentiality of identifiable data, e.g., use of password protections (please refer to the Harvard Research Data Security Policy (HRDSP), at <http://vpr.harvard.edu/pages/harvard-research-data-security-policy>, for additional information about required data security measures) [NOTE: The HRDSP does not always apply if data are not being stored at Harvard facilities. Please consult the HRDSP for additional information.]

Yes: Confidentiality will be maintained via the following. No electronic data will be kept except CDs of the CT scans. Standard of care data will remain in the Axiom system. All research data (the CDs and the hard copy CRFs) will be stored within in a locked cabinet in a locked room (the Periodontology Residents room at HSDM).

2. Describe i) whether data will be transmitted, and if so how; ii) how long it will be stored; and iii) plans for the data at the end of the storage period (how will it be destroyed, or will it be returned to data provider)

i) There will be no transmission of identifiable data.

ii) Standard of care data will be protected under the Axiom software firewall. Research data (hardcopies) will be stored in a locked cabinet within a locked office.

iii) At the end of the study period, the clinical data will be moved to an offsite storage facility for HSDM research data which will then be destroyed after 10 years unless otherwise instructed.

3. Indicate how research team members and/or other collaborators are permitted access to information about study participants

Only three researchers will have access to the identifiable data information which will be kept in a locked cabinet within a locked office.

PI: Eli Machtei DMD

Co-Investigator: David Kim DMD

Other Study Team Member: Heather Wong DDS

Other Study Team Member: Chia-Yu Chen DDS

4. If future use of data, data sharing, ie, required of NIH-funded studies using/generating large-scale human genomic data, or future open access, ie, free availability and unrestricted use, of data is planned or likely, indicate how data will be shared/released.

N/A

16. Costs and Payments

1. Identify any costs that participants may incur during the study, including transportation costs, childcare, or other out-of-pocket expenses

There are no additional study related expenses other than what the patient (or their insurance) would pay for the standard of care. The cost will be approached (and possibly billed to insurance) as any other standard of care procedures at the dental clinic.

Costs that participants may incur during the study

i) Transportation costs (i.e. parking, gas, public transportation)

ii) Opportunity costs (i.e. patients time will be forfeit where they might normally be at work)

iii) The tooth extraction will also be charged to the patient as is usual in standard of care.

iv) The first CT scan will be charged to the patient. The second CT scan will be done for free. The cost of at least one CT scan is normally charged as a part of the standard of care.

Patients will receive the following for free (which are normally charged for as part of the standard of care)

i) Socket preservation surgery

ii) Bone graft material

iii) Collagen membrane

iv) Additional X-rays

v) The second CT scan

2. **Is there any payment or reimbursement that participants may receive during the study?**

No Yes: If yes; specify the amount, method and timing of disbursement. (Please refer to Harvard University Financial Policy on Human Subject Payments at <http://policies.fad.harvard.edu/pages/human-subject-payments>)

No

17. Multi-site Study Management

1. **Is this a multi-site study?**

No Yes: If yes; describe plans for communication among sites regarding adverse events, interim results, protocol modifications, monitoring of data, etc.

No

18. Investigational Drug/Biologic/Device

1. **Does this study involve an Investigational Drug/Biologic/Device?**

No: If no; skip to 19.1

Yes: If yes; identify and describe the drug/biologic/device (e.g., marketing status: Is there an IND/IDE, classification of a device as significant vs. non-significant risk)

No

2. **Describe its administration or use**

N/A

3. **Compare the research drug/biologic/device to the local standard of care**

N/A

4. **Describe plans for receiving, storage, dispensing and return (to ensure that they will be used only for participants and only by authorized investigators)**

N/A

5. **If proven beneficial, describe anticipated availability and cost to participants post-study; plans (if applicable) to make available**

N/A

19. HIPAA Privacy Protections

1. **Are HIPAA privacy protections required? Please note that only Harvard University Health Services and Harvard School of Dental Medicine are covered entities at Harvard. Harvard is otherwise not a HIPAA covered entity. If, however, data is derived from a Covered Entity (e.g. a hospital or community health center), mark 'yes' and address the items below.**

No: If no; skip to 20.1

Yes: If yes; include at least one of the following:

Describe plans for obtaining authorization to access protected health information

Provide the rationale for a waiver of authorization or limited waiver of authorization request

Yes, the study will be conducted at the Harvard School of Dental Medicine, which is HIPAA covered entity at Harvard. Consent for authorization to access protected health information is included in the Consent Form and will be obtained at enrollment into the study.

20. Data and Specimen Banking

1. **Does the study include Data and Specimen Banking?**

No: If no; skip to 21.1

Yes: If yes; identify what will be collected and stored, and what information will be associated with the specimens

Yes: Data that will be obtained will be that of clinical and radiographic nature which is considered not to be sensitive information.

2. Describe where and how long the data/specimens will be stored and whether participants' permission will be obtained to use the data/specimens in other future research projects

During the duration of the study, a CRF will be collected and stored under locked cabinet in the Periodontology resident's room. At the end of the study period, the clinical data will be moved to an off-site storage facility for HSDM research data which will then be destroyed after 10 years unless otherwise instructed. Data will not be used in the future.

3. Identify who may access data/specimens and how

Only four researchers will have access to the identifiable research data information which will be kept in a locked cabinet within a locked office.

PI: Eli Machtei DMD

Co-Investigator: David Kim DMD

Other Study Team Member: Heather Wong DDS

Other Study Team Member: Chia-Yu Chen DDS

Any standard of care data in the dental record will be available to those who would normally have access.

4. Will specimens and/or data be sent to research collaborators outside of Harvard?

No Yes: If yes; describe the plan

No

5. Will specimens and/or data be received from collaborators outside of Harvard?

No Yes: If yes; describe the plan

No

21. Sharing Study Results

1. Is there a plan to share study results with individual participants?

No Yes: If yes; describe the plan

No

2. Is there a plan to disseminate aggregate results to the community where the research is conducted?

No Yes: If yes; describe the plan

De-identified data will be used for statistical analysis and eventually be submitted for publication in a peer review journal in aggregate

22. Regulatory Compliance

1. Describe plan for monitoring regulatory compliance, in order to ensure proper record keeping and retention of required regulatory documents

Patients' private information will be obtained in a private environment and recorded in the CRF that is not available outside of the study investigators. These booklets will be kept within a locked cabinet inside of a locked room. At the end of the study period, the clinical data will be moved to an off-site storage facility for HSDM research data which will then be destroyed after 10 years unless otherwise instructed. Study staff will be responsible for ensuring that regulatory documentation is being kept compliant and will monitor this process at each study visit.