Comparing the Efficacy and Morbidity of Two Vertical Ridge Augmentation Techniques

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I) Introduction

The aim of the randomized prospective controlled clinical trial, a split mouth design, is to compare the efficacy and morbidity of the two vertical ridge augmentation techniques: Titanium mesh (Ti-mesh) technique and Guided Bone Regeneration (GBR) technique using a high-density polytetrafluoroethylene (d-PTFE) membrane. The efficacy will be measured by the height gain (Aim 1) and the bone core histology/histomorphometry (Aim 3). The morbidity will be assessed by the incidence of post-operative complications (Aim 2).

Aim 1: Compare the height gain obtained in vertical ridge augmentation procedures using intrasurgical clinical measurement in millimeter.
We hypothesize that the height gain obtained after the six months healing period following vertical augmentation using Ti-mesh will be more, compared with that of a d-PTFE membrane.

Aim 2: Identify and compare the rate of post-operative complications following vertical ridge augmentation procedures using a complication case report form (CRF).
We hypothesize the incidence of surgical complications occurring in vertical ridge augmentation procedures with Ti-mesh will be less frequent, compared with a d-PTFE membrane.

Aim 3: Evaluate and compare bone core histology by quantifying new bone formation using histomorphometric analysis.
We hypothesize that the new bone formation using vertical ridge augmentation procedures with a Ti-mesh membrane will be greater, compared with d-PTFE membrane.

II) Background and Rationale

Background:

Vertical ridge augmentation is challenging, but an important treatment modality for patients with severely deficient edentulous ridges usually from being edentulous in these areas for an extended period of time. A successful procedure will make implant placement possible by providing new bone formation with improved functional and aesthetic outcomes. Vertical ridge augmentation can be achieved through different methods including Guided Bone Regeneration (GBR) with non-resorbable membrane, onlay autogenous block bone graft, distraction osteogenesis (DO) and Titanium mesh (Ti-mesh) technique.[1-3] Currently, GBR and Ti-mesh techniques are commonly used in the clinical practice because of their less-invasive characteristics compared to other techniques. GBR using non-resorbable membrane with particulated bone graft is supported by a wide range of scientific evidence.[4] In particular, an expanded-polytetrafluoroethylene (e-PTFE) membrane with particulate graft was considered the gold standard of GBR procedure in vertical augmentation.[5-8] However, recently, the traditionally used e-PTFE membrane was discontinued in

the market. A newer non-resorbable membrane, a high-density polytetrafluoroethylene (d-PTFE) membrane has been introduced as an alternative. The main characteristic of the d-PTFE membrane is lower porosity, which is less than 0.2 micrometer pore size on the membrane surface, compared with the e-PTFE. This feature may provide resistance to the membrane against bacteria, and low risk of infection compared with the e-PTFE membrane. The d-PTFE membrane has been used widely for procedures such as ridge preservation after tooth extraction. However there is limited scientific data available evaluating the performance of the d-PTFE membrane in vertical ridge augmentation at the present time. Only a few studies are available with a small number of subjects.[9,10]

Titanium mesh technique with particulate graft is also used for vertical ridge augmentation. The stiffness of the titanium mesh can provide better space maintenance ability compared to a non-resorbable membrane. However, some drawbacks have been reported such as an increased number of mesh exposures and soft tissue ingrowth, which result in less bone regeneration. Only a few studies are available with a small number of subjects to support its applications for vertical augmentation at this time.[11-14]

Rationale:
The proposed study will be the first randomized controlled clinical trial that will investigate the use of d-PTFE membrane compared to Ti-mesh in vertical augmentation. The study will be able to provide scientific evidence that will help clinicians in the decision-making process for vertical ridge augmentation. The split-mouth study design will support a direct comparison between the two surgical techniques. Additionally, this project will benefit TUSDM educationally by creating more interest in the vertical ridge augmentation procedure among the residents, dental students and faculty members. Ultimately, it may improve the quality of care for the patients at TUSDM.

The current literature does not provide evidence-based criteria that indicate one of the two techniques currently used in the clinic. The primary goal of this study is to compare the efficacy by measuring clinical height gain between the two techniques. The secondary goal of the study is to compare the morbidity with patient-centered outcomes research design. The proposed study will help make more informed treatment decisions of patients by providing evidence on the risks and benefits between the treatment options.

TUSDM Periodontology Clinic Standard of Care

A patient who requires vertical ridge augmentation receives either of the two surgical materials, d-PTFE membrane or Ti-mesh, based on the dentist's preference. It is the surgeon's discretion to choose one or the other material based on their experience. The two materials are considered equally effective and no additional risk of one over the other has been reported at TUSDM.

III) Research Plan

A) Experimental Design

The proposed study design is a randomized controlled trial, split mouth design, to compare the two different vertical augmentation procedures: Titanium mesh (Ti-mesh) technique and Guided Bone Regeneration (GBR) technique with a high-density polytetrafluoroethylene (d-PTFE) membrane.

B) Sample Size and Statistical Analysis

Sample Size:

We have used the available data (mean, standard deviation) for the height gain with an anorganic bovine bone (Bio-oss) with e-PTFE membrane or Ti-mesh for the sample size calculation.[6,15] We anticipate that the property of a d-PTFE membrane is similar to an e-PTFE membrane, and the amount of the height gain to be similar between these two membranes.[10]

A power calculation was performed in nQuery Advisor (version 7.0) with the following assumptions: a type I error of 5%; a type II error of 7%; the titanium mesh group has a mean (SD) height gain of 5.2 (0.79) mm (Artzi 2003)[15]; the e-PTFE group has a mean (SD) height gain of 3.15 (1.12) mm (Simion 2007) [6]. The minimum sample size necessary was determined to be 7 subjects. To account for potential dropout, the study population will be increased to include 10 subjects. Up to 15 subjects will be consented (and considered enrolled) into the study to achieve these goals.

Statistical Analysis:
Counts and percentages, will be reported for categorical data. Mean and standard deviations will be reported for continuous data.
1. For the Aim 1, the height gain will be measured in millimeters (mm) and considered to be continuous data. The paired t-test will be used to compare the height gain after the healing following vertical ridge augmentation between the d-PTFE membrane group and the Ti-mesh group.

2. For the Aim 2, the mean incidence of post-operative complication in each group will be measured in percentage as categorical data. The Mann-Whitney U test will be used to compare the incidence of post-operative complications occurred in vertical ridge augmentation procedures between the d-PTFE membrane group and the Ti-mesh group.

3. For the Aim 3, the new bone formation will be measured in percentage as categorical data. The paired t-test will be used to compare the percentage of

new bone formation after the healing following vertical ridge augmentation between the d-PTFE membrane group and the Ti-mesh group.

All analyses will be performed using Stata (version 13.1)

Randomization:
Randomization will be performed in a 1:1 ratio using a balanced design based on a computer-generated randomization scheme, both for the location of the procedure, but also for the performed technique. Randomization will occur during visit 2.

Blinding:
The subjects will be blinded for the randomization assignment (Single-blinded). We will blind subjects by not informing them of their treatment allocation (d-PTFE membrane or Ti-mesh). If subjects do not see the preparation of the materials (d-PTFE or Ti-mesh), they will not be able to tell which procedure they receive. The preparation of d-PTFE membrane and Ti-mesh will be performed and delivered to the surgical site out of sight of participants during surgery.

C) Products

Group	Product 1	Product 2
d-PTFE membrane	Cytoplast™ Barrier Membranes, Osteogenics Biomedical	Bone graft material: Deproteinized bovine bone material (DBBM) Bio-Oss GeistlichPharma North America, Inc.
Ti-mesh	Titanium Mesh, BioHorizons	Bone graft material: Deproteinized bovine bone material (DBBM) Bio-oss GeistlichPharma North America, Inc.

Cytoplast™ Barrier Membranes, Osteogenics Biomedical: Cytoplast has been FDA-approved for use in a space-making barrier. The material will be used in this study for its approved indication.

Titanium Mesh, BioHorizons: Ti-mesh is regulated as a minimally manipulated product. Titanium products such as mesh and screws are commonly used as adjunctive materials in periodontal or oral surgeries. As such, there is no FDA approval process or documentation to be had. Currently, Ti-mesh from BioHorizon is used in the TUSDM clinic.

Deproteinized bovine bone material (DBBM) Bio-oss GeistlichPharma
North America, Inc.: Bio-oss has been FDA-approved as a bone grafting material. The material will be used in this study for its approved indication.

D) Subject Characteristics

Subjects referred to the postgraduate clinic in the Department of Periodontology at Tufts University School of Dental Medicine, that were previously diagnosed with severely deficient edentulous ridges in the bilateral posterior mandible (Seibert Class III) and treatment planned for vertical ridge augmentation and implant placement procedure, will be included in the study. The diagnosis and treatment plan will be established by the undergraduate or postgraduate clinics.

1) Inclusion Criteria

All patients will be required to meet the following inclusion criteria.
(1) 18 years of age or older
(2) Non-smokers
(3) Existence of bilateral vertical/horizontal ridge deformities (Seibert Class III)
(4) The length of the edentulous span is from two or more teeth

2) Exclusion Criteria

The patients will not be admitted in the study if any of the following exclusion criteria are met:

(1) Patients who have an infectious disease (self reported - HIV, tuberculosis or hepatitis)
(2) Known allergies to the research-related materials
(3) Patients who have compromised healing potential:
- bone metabolic disease e.g., Paget's disease, osteoporosis, osteomalacia
- uncontrolled diabetes: HbA1c >=7, values measured within six months (using the existing record in AxiUm or if the subject has the condition, but there is no report in AxiUm – a blood test record will be requested)
- patient currently taking steroid medication
- history of oral bisphosphonate intake greater than 3 years or any IV administration
(4) Pregnant or lactating patients (self-reported), as part of TUSDM standard of care not to treat for non-emergency surgical procedures
(5) Presence of surgical scar tissue from previous surgical procedure in the posterior mandible
(6) Pathology present within the alveolar ridges in the posterior mandible, determined clinically or radiographically
(7) History of radiation therapy to the mandible
(8) Smokers

Elective periodontal procedures are postponed during pregnancy, active infectious disease, bisphosphonate intake or uncontrolled diabetes as standard of care in the TUSDM department of periodontology. Diseases or conditions which have been shown to affect healing are excluded for research. Vertical ridge augmentation is not contraindicated with pregnancy and there is no known safely issues associated with it.

3) Subject Withdrawal/Termination Criteria

(1) Non-compliance.
(2) Unwillingness to further participate.

The Principal Investigator will determine whether withdrawn subjects are in need of additional treatment and/or follow-up observation as a result of participation in this trial. These treatment and/or follow-up appointments will follow standard clinic guidelines of the TUSDM periodontology clinic dependent upon which point the subject was withdrawn from the study.

D) Assessment

1) Risk

The present study has no additional risks to the subjects beyond the normal risks for the surgical procedure as the study involves standard clinical procedures performed at TUSDM periodontology clinic. However, subjects may experience more discomfort and longer surgery time because two surgeries will be done in one day for this study. Usually, either of one augmentation techniques is used at a time for one side from standard clinical practice at TUSDM, because vertical augmentation is technically demanding procedure. However, occasionally, we perform two vertical augmentation procedures at a time for both sides depending on cases in the practice or at TUSDM.

The present study presents various complications that are possible with the vertical ridge augmentation procedures, both with a d-PTFE and titanium mesh. The common complications that can occur are: exposure of d-PTFE membrane or titanium mesh, infection, paresthesia, postoperative pain, swelling and bleeding. However, there is no additional risk participating in the study compared to the standard of care of vertical ridge augmentation. d-PTFE membrane cannot be used under load bearing conditions, which is not related to the study procedure.

As with surgeries involving metallic implants there is a chance for foreign body sensitivity. Where material sensitivity is suspected appropriate tests should be made to rule out this possibility prior to implantation.

Risk of bone core biopsy

In the bone core biopsy, a trephine will be used and a bone core sample of the hard tissue will be collected and finalized with standard bur prior to implant placement. No more than the standard amount of bone will be removed for this study. There is no additional risk related to this procedure. The risk associated with bone biopsy is over-drilling of bone (create a bigger hole than the size of hole that is necessary for bone core) when harvesting a bone piece. However, the risks associated with bone biopsy are minimal because a bone core drill is smaller than a standard implant drill, which is necessary to place an implant.

2) Benefits
There is no medical benefit to the subject for participating in this study.

3) Alternatives
Study subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their dental care. The alternative is not to participate in the study. Patients may receive the standard care for vertical augmentation procedures from postgraduate students of the TUSDM periodontology clinic at standard clinic fees.

E) Study Procedures

Visit 1: Screening

Informed consent will be obtained by the principal investigator or a co-investigator. The subjects will be instructed to read the informed consent form (ICF), given ample time to have any questions answered, and then instructed to sign the ICF. Subject will be given a copy of the ICF.

Subject will be asked to complete demographic information and a medical history.

Inclusion/exclusion criteria will be evaluated.

The pre-operative height of the bony crest will be evaluated on the pre-existing radiographs from the referring clinic if they are less than 6 months old. If recent radiographs do not exist, radiographs will be taken at this visit. Regardless of the subject's involvement in the study, it is standard of care to have radiographs taken within the past 6 months prior to surgery.

Visit 2: Surgery

Medical history will be reviewed as standard of care.

Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

Surgeries will be performed by either of two investigators.

The use of d-PTFE for vertical ridge augmentation will be randomly assigned to one side of the mouth of each subject (randomization is for research purposes) and Ti-mesh to the other side of mouth, and therefore, subjects will receive both of the following procedures:

*Guided Bone regeneration (GBR) procedure using a d-PTFE: (standard of care excluding clinical measurements)
The following steps will be performed following standard of care procedures: local anesthesia, muco-periosteal incision, full thickness flap reflection, de-cortication of the alveolar ridge, bone harvesting using bone scrapers, tenting screw placement, clinical measurements, DBBM graft material placement, the placement and stabilization of the d-PTFE membrane according to manufacturer's instructions, sutures.

* Guided Bone regeneration (GBR) procedure using Ti-mesh: (standard of care excluding clinical measurements)
The following steps will be performed following standard of care procedures: local anesthesia, muco-periosteal incision, full thickness flap reflection, de-cortication of the alveolar ridge, bone harvesting using bone scrapers, tenting screw placement, clinical measurements, DBBM graft material placement, the placement and stabilization of the titanium mesh according to manufacturer's instructions, sutures.

Bone harvesting using bone scrapers will be performed during GBR procedures with both techniques (d-PTFE and Ti-mesh). Bone harvesting using bone scrapers is for harvesting particulate autogeneous bone graft material. We will use a mixture of 50:50 DBBM and autogenous bone graft material for all vertical augmentation procedures in the study. Particulate autogenous bone graft will be harvested from the retromolar region of the mandible. This area is just next to the area of GBR procedures (posterior mandible) and will be visible after flap elevation for vertical augmentation. Therefore, we do not need any additional steps except harvesting autogenous bone graft. Intraoral harvesting by bone scrapers from the retromolar region is a simple and safe method for collecting cortical bone chips.

The intrasurgical clinical measurements of the ridge height will be taken during surgery. The distance between the top of the tenting screw and bone crest will be measured with a periodontal probe during the procedure. Duration of each procedure and surgical complications including flap tear and bleeding will be collected. All outcome measurements will be performed by a Co-I who did not perform the surgery.

The subject will be asked to complete a pain/discomfort survey using VAS scale from zero to ten. A medication log will be given to the patient to track the number of pills of the prescribed painkiller they have taken in order to examine the amount of pain after the surgical procedures. The mean number of pills used after surgical procedures will be analyzed.

Post-operative medication will be prescribed following TUSDM standard of care guidelines.

Visit 3 (7±3 days after procedure): Post-operative Follow-up

Medical history will be reviewed as standard of care. Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

Each subject will have a post-operative visit, which is standard practice at TUSDM periodontology clinic. Standard of care procedures including suture removal and evaluation of surgical site will be performed.

For research, information regarding bleeding, presence of infection, bruising, and/or other complications will be collected. Each subject will complete a survey to evaluate the level of pain/discomfort, bleeding, and swelling following the surgical procedure for each side – each classified on a VAS scale from zero to ten. In addition, the subject will return his or her completed medication log.

Visit 4 (21±3 days after procedure): Post-operative Follow-up

Medical history will be reviewed as standard of care. Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

Each subject will have a post-operative visit, which is standard practice at TUSDM periodontology clinic. Standard of care procedures including suture removal and evaluation of surgical site will be performed.

For research, information regarding bleeding, presence of infection, bruising, and/or other complications will be collected. Each subject will complete a survey to evaluate the level of pain/discomfort, bleeding, and swelling following the surgical procedure for each side – each classified on a VAS scale from zero to ten.

Follow-up visits during the six month post-operative period of the vertical ridge augmentation surgery will be scheduled. Standard of care procedures and evaluations will be completed during follow-up visits. The surgical sites will be evaluated after the vertical ridge augmentation procedures, in order to assess the presence of postoperative complications, such as the exposure of a d-PTFE membrane or Ti-mesh, infection, swelling, paresthesia or any other complications. All will be noted in the subject's axiUm record and reviewed at the time of Visit 4.

Visit 5 (6±1 months after Visit 4): Evaluation visit

Medical history will be reviewed as standard of care. Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

Surgical sites will be evaluated and the subject's axiUm record will be reviewed for any complications.

Each subject will complete a survey to evaluate the level of pain/discomfort, bleeding, and swelling following the surgical procedure for each side – each classified on a VAS scale from zero to ten, as at Visit 3.

Radiographs will be taken. It is standard of care to have radiographs taken prior to implant placement. The post-operative (after the vertical GBR augmentation procedure) height of the bony crest will be evaluated on the radiographs taken as part of standard of care.

Visit 6 (Up to 1 month after Visit 5): Bone core harvesting, implant placement visit

Medical history will be reviewed as standard of care. Eligibility and subject withdrawal criteria will be reviewed to ensure the subject still qualifies for the study.

The subject will present for their regularly scheduled implant placement. The following steps will be performed following standard of care procedures: local anesthesia, muco-periosteal incision, full thickness flap reflection, membrane (Ti-mesh/d-PTFE) removal, clinical measurements, tenting screws removal, bone core harvesting, implant osteotomy, implant placement, and sutures.

The intrasurgical clinical measurements of the ridge height will be taken at during implant placement surgery. The distance between the top of the tenting screw and bone crest will be measured with a periodontal probe during the procedure. The bone height gain will be calculated by subtracting the second measurement form the first measurement (taken during initial surgery).

At the time of the implant placement a bone core will be harvested from each site of the implant locations for histological analysis. For the bone samples in this study, a hollow (trephine) bur, rather than solid bur, will be used to allow for sampling. A trephine bur with 3-4 mm diameter will be used. The core size will not exceed the amount of bone removal required for designated implants. Removal of bone is standard during implant placement in order to create space for the fixture.

The bone core biopsies will be placed in fixative and labeled with subject ID. The collected bone samples will be placed in alcohol for storage and stored in a basic science laboratory DHS-635.

The implant placement will not be considered a part of this study.

After Visit 6 - Laboratory analysis of bone core sample

Histological slides will be prepared and histomorphometric analysis will be performed by the commercial laboratory. The samples will be coded as subje ct numbers and histological analysis will be blinded. All collected bone core sa mples will be shipped to the laboratory by PI or Co-I.

Histomorphometric measurements of the tissue fractions (DBBM, autogenous bone, newly formed bone and marrow and/or connective tissue) will be performed for the grafted area. The sections will be digitally photographed with computerized software.

Table 1. Subject Timeline

	V1	**V2**	**V3**	**V4**	**V5**	**V6**
	Screening	Surgery	1 week Evaluation	3 week Evaluation	6 month Evaluation	Bone Core Biopsy
Consent	X					
Evaluation of eligibility	X	X	X	X	X	X
Medical History	X	X	X	X	X	X
Pre-operative Radiograph Evaluation (radiographs taken if necessary)	X					
Randomization		X				
Surgery		X				
Clinical Measurements		X				X
Patient VAS Scoring		X	X	X	X	
Medication Log Given/Collected		X	X			
Complication Evaluation			X	X	X	
Post-operative Radiographic Evaluation (radiographs taken)					X	
Bone Core Harvesting						X
Adverse Event Assessment		X		X	X	X

F) Subject Safety

1) Adverse Event Reporting

Adverse Events
An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with a subject's participation in the research.

Adverse events will be recorded in source documents and on case report forms. All adverse events and non-serious situations will be recorded, monitored, and reported to the IRB at time of continuing review and at the time of the study's termination. Subjects experiencing an adverse event will be evaluated by the PI to determine if it is safe for them to continue in the study. If continuation in the study poses any additional risks, the subject will be withdrawn from the study.

Serious Adverse Events
A serious adverse event is one that results in death, or is life-threatening, or results in hospitalization or prolongation of existing hospitalization, or results in a persistent or significant disability/incapacitation, or results in a congenital anomaly/birth defect, or may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

Serious adverse events will be recorded in source documents and on case report forms. Serious Adverse Events will be reported to the IRB within 15 business days.

Unanticipated Problems
An unanticipated problem is an incident, experience, or outcome that meets all of the following criteria: 1) The nature, severity, or frequency is unexpected for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the ICF(s); 2) it is related or possibly related to participation in the research; 3) it suggests the research may place the subject or others at a greater risk of harm then was previously recognized.

Unanticipated problems will be recorded in source documents and on case report forms. Unanticipated problems will be reported to the IRB within 5 business days. An initial report will be submitted to the IRB no later than 2 business days after the PI/study team become aware of the problem, as well.

2) Reporting

Notification of the IRB of any protocol deviation, including to protect the life or physical well being of a subject in an emergency, shall be given to the IRB as they occur throughout the course of the study.

Progress reports on the investigation shall be submitted to the IRB at regular intervals, but in no event less often than yearly.

A final study report shall be submitted to the IRB following termination or completion of the study. Study completion will be defined as completing assessments on the last subject.

G) Subject Participation

1) Screening

The principal investigator or her representative will conduct screening examinations to identify subjects who meet the inclusion/exclusion criteria for enrollment into the study.

2) Informed Consent

The principal investigator or her representative will introduce the study.

Consenting will take place in a private clinic bay area and the patient will be given as much time as he/she needs to consider participation. The participant will be invited to include or exclude any associates (e.g., loved ones) in the consent process.

Patients will be asked to read the consent form and given ample opportunity to have their questions answered. To avoid coercion, the consenting investigator will read through the copy of the consent form with the participant section by section, making sure the participant understands each section and has an opportunity to ask questions. If at any time the participant indicates s/he is not interested in participation, the meeting will end.

If after going through the consent form, the participant indicates s/he would like to discuss the study with associates or think about participating, then the meeting will be ended and the participant will be asked to contact the study when s/he makes her decision. If the participant contacts the study in the future for participation, s/he will be invited back to the clinic, and if informed consent is given at that time, study activities will begin then.

If the participant indicates s/he may be interested in participating after going through the consent form with the investigator, and the investigator determines the participant has the capacity to provide informed consent, the participant will be asked to provide informed consent at that time. Patients will certify their willingness to participate in the study by signing

and dating the IRB approved informed consent document. The subject will be given a copy of the consent form.

If any new finding requires any change to the informed consent form, the subject will be reconsented.

Non-English speaking subjects will not be enrolled in the study because study staff at this time are not certified, prepared, or trained to translate or communicate in any language other than English. The study budget does not allow for the payment of translation services at this time.

3) Study Location
TUSDM

4) Personnel
The PI will be responsible for ongoing communication with the IRB.

PI or Dr. Co-I will perform all surgical procedures including bone biopsy. The Co-I will perform clinical measurements, surveys and follow-up visits.

PI or Co-*I* will be responsible for obtaining informed consent. The consent process will be begun by PI, medical Co-I, or a research coordinator. If a research coordinator begins the consent process, PI or medical Co-I will complete it.
PI or medical Co-I will be available to answer any medical questions.
PI, Co-I, or a research coordinator will be responsible for maintaining records.

The research coordinating team at TUSDM have worked on numerous clinical studies and have a history of performing the consent process with subjects and assessing competency. They are CITI education certified and GCP trained. In addition, they have attended multiple trainings related to these tasks.

5) Payment for Participation
(a) Compensation
Subject will not be charged a fee of $738 for each bone augmentation surgery.

If re-do of the procedure is necessary due to infection or additional need for bone grafting, the second procedure will be provided at no cost.

Subject will not be charged surgical fee of $1,165 for one implant.

The reduction in surgical fees (both the bone augmentation surgery and implant surgery) will go into effect at the time of the visit. The subject will pay the reduced surgical fees at the time of the visit.

If the subject is in need of placement of any additional implants, he/she and/or their insurance will be responsible for the cost.

Subject will be responsible for covering the fees for the later implant crown procedures (which are not a part of this study).

If a subject withdraws or is withdrawn from the study, the reduction in fees will only apply for the time prior to the withdrawal.

(b) Transportation
No travel reimbursement and transportation costs will be provided.

(c) Payment and Insurance
If the patient has insurance policy that covers the fee of additional implants, he or she will be responsible for the co-payment only.

6) Study Results
If interested, study results will be presented to a subject upon his/her request. Study results will be given to a subject in person or via mail, according to the subject's preference, upon completion of the study. A log will be kept of the participants who are interested in receiving study results. Identifying screen failure data will be retained by the PI. Data from screen failures will be retained in the locked cabinet in the PI's office at TUSDM.

7) Confidentiality
To ensure confidentiality of subject information, each subject enrolled in the study will be assigned a unique alphanumeric code. Subjects' files will be kept in a secure, locked cabinet, within a locked room (DHS-1256) when the files are not reviewed. The information will only be shared between the researchers. All HIPAA requirements will be followed. All electronic files will be kept on a password protected computer in a secure, locked office.

a) Coding
Each subject will be assigned a subject identification number. Alphanumeric identification numbers will be assigned sequentially. This will be accessible by study personnel only. Dental records and case reports used in this study will be coded and will not include subject names.

b) Access

Only study personnel will have access to data. Investigators will permit monitoring, audits, and regulatory inspections and will provide direct access to study related documentation.

c) Publication
If any publication results from this study, subjects will not be identified by name without their written consent.

8) Data Safety Monitoring Plan:
Study personnel will monitor this trial for all safety related issues to determine whether an unreasonable risk to subjects develops. Quality control measures include routine inspection of case report forms, source documents, data tabulations, and tracking of adverse events.

9) New Findings
The subject will be informed of any significant new findings discovered during the course of this study that might influence the subject's continuation and participation in the study. Subjects will be told at a study appointment or via telephone of new findings during the study.

If new findings require revisions to the ICF, the subject will be re-consented.

H) Record Retention

1) Study Records
The investigators will maintain all study records and documents during the study period. All paper files and documents will be kept in a locked file cabinet, within a locked room (DHS-1256). Electronic records will be kept on a password protected computer will only be accessible to study personnel.

2) Long Term Retention
The investigator will maintain all study records following completion or termination of this study in accordance to state law and institutional policy (at least 7 years after the study is completed or terminated).

I) Reporting
Unanticipated problems and adverse events will be reported per the Tufts MC/TUHS IRB Unanticipated Problem and Adverse Event Reporting Policy.

The IRB will be notified of any deviations from the protocol in cases of medical emergencies when the change is necessary to eliminate an apparent immediate hazard to the subject

Progress reports on the investigation shall be submitted to the IRB at regular intervals, but in no event less often than yearly, e.g., at continuing review.

J) Protocol Deviations

No protocol changes or deviations will be made without prior agreement by the IRB unless implemented to prevent an immediate hazard to subjects. All other protocol changes or deviations will be made by a formal amendment subject to IRB approval. All such changes or deviations will be reported to the IRB as they occur and included in the final study report.

K) Study Termination

This study may be terminated for the following reasons:

Discovery of unforeseen risk that could jeopardize the dental/physical well being of subjects.

Enrollment or recall rates that are not likely to produce sufficient data for evaluation of safety and efficacy

Non-compliance with the clinical investigational plan, the Investigator Agreement, applicable FDA regulations or conditions of approval imposed by the reviewing IRB

Withdrawal of IRB approval

In the event of study termination, the Principal Investigator will determine whether subjects are in need of additional treatment and/or follow-up observation as a result of participation in this trial.

L) Subject Recruitment/Advertising

Paper flyers will be posted throughout TUSDM. Permission is not required for these posting locations. Flyers will remain posted until enrollment goals are met. Subjects will be recruited through responding to posted study advertisements.

Investigators may also inform clinic patients about the study.

Investigators may send messages to colleagues via axiUm asking for their help in recruiting eligible subjects.

Likewise, e-mails and/or newsletters that alert the TUSDM community to ongoing studies may include information on this study for recruiting purposes.

Forms of electronic media such as twitter, university websites, Facebook, Craigslist, etc. may also be used to recruit.

All of the forms of recruitment will be submitted for IRB approval prior to use.

A screening interview/questionnaire or screening script will be used for recruitment.

Screen failure data will be retained by PI. Screening ID number and demographic information will be recorded. Identifiable information will not be recorded in the screening log.

M) References/Bibliography

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