COVER PAGE

Official Study Title: Randomized controlled trial of wound healing following tooth extraction and ridge preservation using demineralized freeze-dried bone allograft (DFDBA) in cortical particulate form versus fiber form

NCT number: NCT05400213

IRB Approval Date: 06.14.2022

Unique Protocol ID: 20220346H

Form CT
UTHSA Clinical Trial Description

This form is not mandatory. Other documents are acceptable if equivalent information is provided.

UTHSCSA Tracking Number *(internal use only)*	HSC20220346H	**1. Original Version Date**	V1.0, 2022-05-31
		1.1. Revision Date(s) *add rows as needed*	

Title: Randomized controlled trial of wound healing following tooth extraction and ridge preservation using demineralized freeze-dried bone allograft (DFDBA) in cortical particulate form versus fiber form

2. Background

Briefly discuss the important literature relevant to the trial and that provides background for the trial. Include the importance of the trial and any relevant treatment issues or controversies.

Bone grafting following tooth extraction is performed to preserve bony ridge dimensions adequate to allow subsequent implant placement in a proper restoratively-driven position. Alveolar ridge resorption commonly occurs following tooth extraction, and the decrease in bone volume has the potential to make dental implant therapy impossible without surgery to reconstruct the ridge. The aim of ridge preservation grafting is to prevent or minimize this resorptive process, thereby preserving satisfactory bone volume for implant placement, while also obtaining an adequate amount of new vital bone formation to support implant integration. Ridge preservation generally involves placement of a bone graft material in the tooth socket, followed by use of a membrane or wound dressing over the socket entrance to contain the bone graft.

Various grafting materials have been recommended for ridge preservation procedures, including cortical and cancellous freeze-dried bone allograft (FDBA), demineralized freeze-dried bone allograft (DFDBA), and various xenografts, alloplasts and autografts. Our research group in the Department of Periodontics at the UT Health San Antonio School of Dentistry has spent over 15 years evaluating wound healing and clinical changes in ridge dimension following ridge preservation procedures using a variety of bone grafting materials and treatment protocols.[1-19] In many of these studies, bone allografts were used for ridge preservation[2,3,5,8,-13,15-19], while in others xenograft was used.[4,14] Our research has generally involved the histologic evaluation of wound healing after ridge preservation as the primary outcome measure, with the main parameters of healing being the percentage of new vital bone formation, residual bone graft material and connective tissue/other (CT/other) non-bone material at the ridge preservation site. We have used different bone replacement graft materials, wound barriers, and regenerative membranes to discern any differences in wound healing with numerous techniques at various time points after ridge preservation. Our studies have also evaluated clinical or radiographic changes in ridge dimension (vertical ridge height and horizontal ridge width changes) as secondary outcomes.

In two studies, we compared 100% cortical mineralized FDBA, 100% cancellous mineralized FDBA and a combination of 50% cortical with 50% cancellous mineralized FDBA and found no significant difference in new bone formation between groups at 18 to 20 weeks post-ridge preservation.[5,12] Because demineralized FDBA has been used in periodontics for decades, Wood & Mealey[3] compared demineralized FDBA to mineralized FDBA for ridge preservation and found significantly greater vital bone with DFDBA formation (38.4%) compared to mineralized FDBA (24.6%) at 18 to 20 weeks post-ridge preservation. Due to these positive outcomes with DFDBA, Whetman & Mealey[9], then examined earlier healing time points after ridge preservation using DFDBA. An average of 47% vital bone was found at 18 to 20 weeks of healing, but as early as 8 to 10 weeks after grafting, 32% vital bone was already present.

Over the past several years, combination allografts that include both mineralized and demineralized FDBA have become available, and our study group has evaluated these materials in several randomized controlled clinical trials. Borg and Mealey[8] used a combination allograft (70% FDBA:30% DFDBA) compared to 100% FDBA and found greater vital bone formation in the 70%:30% group (36%) compared to FDBA alone (24%) at 18 to 20 weeks of healing. The robust vital bone formation found with the 70% FDBA:30% DFDBA combination allograft led to a study evaluating healing at earlier time points. Nelson and Mealey[12] found that using a combination allograft of 70% FDBA:30% DFDBA resulted in 18% vital bone at 8 to 10 weeks, compared to 40% vital bone at 18 to 20 weeks, over twice the amount of vital bone formation with a longer healing time.

Systematic reviews and meta-analyses have examined ridge dimensional changes following ridge preservation procedures.[20,21] Our study group also evaluates changes in ridge dimension in each of our studies using various materials and protocols for ridge preservation.

Recently, non-particulate allograft products have become available for use in periodontal, implant, and oral surgical procedures. Most of these materials have little human wound healing data when they are used for ridge preservation after tooth extraction. In addition, there few published studies of wound healing results after ridge preservation performed combinations of xenograft and allograft materials.

References:

1. Beck TM, Mealey BL. Histological analysis of healing after tooth extraction with ridge preservation using mineralized human bone allograft. *Journal of Periodontology* 2010; 81: 1765-1772.
2. Hoang TN, Mealey BL. Histological comparison of healing following ridge preservation using human demineralized bone matrix putty with one versus two different sized bone particles. *Journal of Periodontology* 2012; 83: 174-181.
3. Wood RA, Mealey BL. Histological comparison of healing following tooth extraction with ridge preservation using mineralized vs. demineralized freeze dried bone allograft. *Journal of Periodontology* 2012; 83: 329-336.
4. Cook DC, Mealey BL. Histological comparison of healing following tooth extraction with ridge preservation using two xenograft products. *Journal of Periodontology* 2013; 84: 585-594.
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6. Coomes AM, Mealey BL, Huynh-Ba G, Barboza-Arguello C, Moore WJ, Cochran DL. Buccal bone formation after flapless extraction: A randomized controlled clinical trial comparing recombinant human bone morphogenetic protein-2/absorbable collagen carrier and collagen sponge alone. *Journal of Periodontology* 2014; 85: 525-535.
7. Frost NA, Banjar AA, Galloway PB, Huynh-Ba G, Mealey BL. The Decision-Making Process for Ridge Preservation Procedures Following Tooth Extraction. *Clinical Advances in Periodontics* 2014; 4: 56-63.
8. Borg T, Mealey BL. Histological comparison of healing following tooth extraction with ridge preservation using mineralized freeze dried bone allograft alone versus a combined mineralized-demineralized freeze dried bone allograft. *Journal of Periodontology* 2015; 86: 348-355.
9. Whetman J, Mealey BL. Effect of healing time on new bone formation following tooth extraction and ridge preservation with demineralized freeze-dried bone allograft. A randomized controlled clinical trial. *Journal of Periodontology* 2016; 87: 1022-1029.
10. Demetter RS, Calahan BG, Mealey BL. Histologic evaluation of wound healing following ridge preservation with cortical, cancellous, and combined cortico-cancellous freeze-dried bone allograft. A randomized controlled clinical trial. *Journal of Periodontology* 2017; 88: 860-868.
11. Corning PJ, Mealey BL. Ridge preservation following tooth extraction using mineralized freeze-dried bone allograft compared to mineralized solvent-dehydrated bone allograft. A randomized controlled clinical trial. Submitted to *Journal of Periodontology* March 2018.
12. Nelson A, Mealey BL. Impact of healing time on wound healing following ridge preservation using a 70/30% combination of mineralized and demineralized freeze-dried bone allograft. A randomized controlled trial. *Journal of Periodontology* 2020; 91: 1256-1263.
13. Walker CJ, Prihoda TJ, Mealey BL, Lasho DJ, Noujeim M, Huynh-Ba G. Evaluation of healing at molar extraction sites with and without ridge preservation A randomized controlled clinical trial. *Journal of Periodontology* 2017; 88: 241-249.
14. Lai V, Mealey BL. Ridge preservation following tooth extraction using porcine and bovine xenograft materials. A randomized controlled trial. *Journal of Periodontology* 2020; 91: 361-368.
15. Al Harthi SM, Prihoda TJ, Mealey BL, Lasho DJ, Noujeim M, Huynh-Ba G. Healing at molar extraction sites using freeze dried bone allograft and collagen wound dressing: Case series and three-arm analyses. *International Journal of Oral and Maxillofacial Implants 2019;* 34: 1202-1212.
16. Duong M, Mealey BL, Walker C, Al-Harthi A, Prihoda T, Huynh-Ba G. Evaluation of healing at molar extraction sites with and without ridge preservation: A three-arm histologic analysis. *Journal of Periodontology* 2020; 91: 74-82.
17. Al Hugail, A. M., Mealey , B.L., Al-Harthi, S., Walker, C., Duong, M., Noujeim, M., Lasho, D.J., Prihoda, T., Huynh-Ba, G. Evaluation of healing at molar extraction sites with ridge preservation using a non-resorbable dense polytetrafluoroethylene (dPTFE) membrane: A four-arm cohort prospective study. *Clinical and Experimental Dental Research* 2021; 7: 1103-1111.

18. Allen HT, Zellner JW, Kotsakis GA, Mealey BL. Long-term preservation of ridge dimension following tooth extraction and ridge preservation: A randomized controlled trial of healing at 4-month and 12-month healing time points. *Journal of Periodontology* (in press).
19. Zellner JW, Allen HT, Kotsakis GA, Mealey BL. Wound healing after ridge preservation: A randomized controlled trial on short-term (4 months) versus long-term (12 months) histologic outcomes after ridge preservation. (in preparation for *Journal of Periodontology*).
20. MacBeth N, Trullenque-Eriksson A, Donos N, Mardas N. Hard and soft tissue changes following alveolar ridge preservation: a systematic review. *Clinical Oral Implants Research* 2017; 28: 982-1004.
21. Troiano G, Zhurakivska K, Lo Muzio L, Laino L, Cicciu M, Lo Russo L. Combination of bone graft and resorbable membrane for alveolar ridge preservation: A systematic review, meta-analysis and trial sequential analysis. *Journal of Periodontology* 2018; 89: 46-57.

3. Objectives and Endpoints *All data points collected in the study should support an objective or have a regulatory purpose.*
Complete the table – add rows as needed.

3.1. Objective(s) *Clearly and concisely define the primary and secondary outcomes.*	**3.2. Endpoint** *Clearly define the endpoints. (endpoints are the basis for concluding that the objective has been met).*	**3.3. Justification for Endpoint** *Briefly explain why the endpoint(s) were chosen.*
Primary Histologic Outcome	% vital bone formation	% vital bone formation shows the amount of new bone formed after the procedure. The higher this % is the better the healing of the site
Secondary histologic outcomes	% residual graft material, and % "CT/other" (fibrous tissue and marrow space)	% residual graft material shows how much of the graft material remained intact. Ideally all the graft materials should turn over to vital bone % CT/other (fibrous tissue and marrow space) is the amount of tissue that is neither native bone or graft material. It may be connective tissue that will mature to osteoid and bone or marrow space that is part of the normal healing
Secondary Clinical outcomes	Change in ridge width; Change in buccal ridge height; Change in lingual ridge height	Clinical measurements show effects of procedures on dimensional changes in the alveolar ridge during healing

4. Rationale
Briefly state the reason for conducting the clinical trial.

Allografts and xenografts are commonly used in ridge preservation procedures. Demineralized freeze-dried bone allografts (DFDBA) are available in particulate and fibers forms. Newer products on the market combine xenografts and DFDBA, but there are little data on histologic healing. Our group is known for this type of research, and we wish to determine if DFDBA fibers result in similar or different histologic outcomes than DFDBA particulate, and whether bovine-derived xenograft combined with DFDBA fibers result in similar or different histologic outcomes than xenograft combined with DFDBA particulate. Finally, we will be able to assess histologic outcomes when particulate DFDBA is used alone versus when it is combined with xenograft and when DFDBA in fiber form is used alone versus when it is combined with xenograft.

5. Study Design

5.1. Number of Groups/Arms	4	**Group name(s)**	1. Group 1: DFDBA particulate at 125-850 micron size (Vallos) 2. Group 2: Xenograft (Bio-Oss) combined with DFDBA particulate at 125-850 micron size (Vallomix) 3. Group 3: DFDBA fibers (Vallos-F)

			4. Group 4: Xenograft (Bio-Oss) combined with DFDBA fibers (Vallomix-F)

5.2. Overall Design
Select all applicable

X	**Randomization**			**Cluster Randomized**							
	Group-Sequential			**Adaptive Design**							
X	**Parallel Design**			**Placebo-Controlled**							
	Superiority			**Equivalence**				**Non-inferiority**			
	Device		Pilot		Pivotal		X	Post-Approval			
	Drug/Biologic		Phase 1		Phase 1/2		Phase 2		Phase 2/3		Phase 3		Phase 4
	Dose escalation	*If yes, details →*									
	Dose ranging	*If yes, details →*									
	Sub-studies	*If yes, details →*									

5.3. Other Design Details:

This protocol summary is for a study entitled, "**A 4-arm randomized controlled trial of wound healing following tooth extraction and ridge preservation using DFDBA alone in particulate or fiber form, and in combination with xenograft**." The primary aim of the study is to determine the amount of newly formed vital bone, residual graft material, and "connective tissue/other" 18 to 20 weeks after ridge preservation is performed using DFDBA fibers alone, DFDBA particulate alone, a combination of xenograft and DFDBA particulate, or a combination of xenograft and DFDBA fibers. The study only involves use of these FDA-approved materials in an FDA-approved manner (for ridge preservation).

The study is a 4-arm, parallel-design, randomized, prospective clinical trial. The study is designed to examine histologic wound healing 18 to 20 weeks following ridge preservation. The study arms include:

1. Group 1: DFDBA particulate at 125-850 micron size (Vallos)
2. Group 2: Xenograft (Bio-Oss) combined with DFDBA particulate at 125-850 micron size (Vallomix)
3. Group 3: DFDBA fibers (Vallos-F)
4. Group 4: Xenograft (Bio-Oss) combined with DFDBA fibers (Vallomix-F)

The patient and the individual doing histomorphometry will be blinded as to study group allocation. The surgeon cannot be blinded in this study.

Null hypothesis: There will be no significant between-group difference in vital bone formation after ridge preservation.

Based on power analysis and drop-out experience from previous studies, we plan to ask our IRB for approval to enroll 30 patients in each of the 4 study groups, with a total of 120 patients for the 4 study groups combined.

All of the bone graft material and overlying membrane material will be provided by Geistlich Biomaterials. To eliminate variability that might occur if more than one human donor's tissue is used in the study, **all of the DFDBA graft material for all treatment groups will be derived from a single human donor**. **The DFDBA graft material will be tested for inductivity by the tissue bank (DCI Donor Services Tissue Bank)**.

All patients will have a single non-molar tooth extracted. Following extraction, patients will be randomized to one of the 4 treatment groups. Clinical ridge measurements will be made using a custom-made thermoplastic measurement stent, and ridge preservation will be performed using one of the materials listed above, per assigned study arm. After graft placement, the graft material will be covered with a resorbable collagen membrane (Bio-gide) membrane (Geistlich Biomaterials) and the site will be sutured with resorbable sutures without attempt at primary closure.

Patients will return 1 to 3 weeks after ridge preservation for post-operative evaluation, and thereafter as indicated by clinical findings. Following the 18 to 20-week wound healing period, a core biopsy will be harvested from the site at the time of implant placement. Just prior to the core biopsy, clinical ridge measurements will again be made using the customized measurement stent.

The core biopsy will be evaluated histomorphometrically for the **primary outcome**: % vital bone formation. **Secondary histologic outcomes** include % residual graft material and % "CT/other" (fibrous tissue and marrow space). The histomorphometric

evaluation will be performed blindly, as the cores being examined will be de-identified as to study arm. In line with our other studies, we will also evaluate the following **secondary clinical outcomes** for each subject: change in ridge width; change in buccal ridge height and change in lingual ridge height.

DETAILED DESCRIPTION OF METHODS:
In keeping with the protocol our study group has used numerous times before, the plan is to extract non-molar teeth and graft with the various graft materials. Each subject will provide a single non-molar tooth site for study treatment. Following approx. 18-20 weeks of healing, we will harvest a core biopsy at the time of implant placement. The implant osteotomy is prepared with a trephine drill and the core inside the trephine is placed in 10% formalin for future processing and histomorphometric analysis. The core biopsy will be evaluated for the primary histologic outcome of % vital bone formation and the secondary histologic outcomes of % residual graft material, and % "CT/other" (fibrous tissue and marrow space). We will also evaluate the following secondary clinical outcomes using a custom measuring stent for each subject: change in ridge width; change in buccal ridge height and change in lingual ridge height. During the 18 to 20-week healing period, patients will be followed as needed per standard care to evaluate healing.

A detailed visit by visit outline is provided below:

Step-by-Step Methods: All the procedures are routinely performed in the graduate periodontics clinic as part of standard care. The methodology is the same previous studies of our group HSC20130470H, HSC20150708H, HSC20170339H, HSC20170267H, HSC2019-0455H, among others.

Visit 1 - Screening examination:
If a patient presents at a consultation appointment at the graduate periodontics clinic with a non-molar tooth (incisors, canines, premolars) that needs to be extracted and replaced with a dental implant, the treating doctor will provide:

- Explanation to the patient of the purposes of the study and the planned procedures related to the study.
- Explanation to the patient of the risks, benefits and possible complications of participation in the study.
- Notification to the patient that inclusion in the study is voluntary and that they will still receive standard of care treatment if they choose not to participate, and conditional upon satisfying the inclusion and exclusion criteria.

Patients will be given the opportunity during the appointment to ask any question that they may have. Following an informational discussion with the prospective subject, consent will be obtained within 2 weeks. This is up to the discretion of the patient. If the patient would like to become a subject for entry into the study, he or she can do so immediately, or can consider it for up to 2 weeks (must be prior to extraction).

Visit 2 – Extraction with ridge preservation using one of the 4 materials described above. All materials are FDA approved and will be used in an FDA approved manner. If the patient has agreed to participate in the study, informed consent will be obtained and documented on a written consent form. If not, standard care treatment will be provided to the patient, and the patient would not be included in the study. Patients will be assigned to one of the 4 groups by randomization with a 1:1 ratio.

On the day of the planned tooth extraction, the medical history will be updated.

Pregnant women or women intending to become pregnant during the study period: Prior to dental surgery, females of child-bearing age are asked verbally if there is any possibility that they are pregnant. If not, we proceed with surgery and no pregnancy test is done. If the woman states that there is a possibility that she is pregnant, an over-the-counter urine pregnancy test to rule pregnancy in or out will be provided. Use of the urine pregnancy test is only done if she says she may be pregnant. [If needed: Urine pregnancy test will be provided to female subjects in the graduate periodontics clinic of UTHSCSA and a negative result is required to enter the study.]

Prior to extraction, impressions of the arch with the tooth to be extracted in place will be taken and poured in stone to obtain initial study casts (research). A clear suck-down resin measuring stent will be fabricated in the laboratory to allow standardization of the location of clinical measurements of ridge width and height through small holes that will be placed in the stent at the time of tooth extraction.

A pre-operative periapical radiographic image will be taken before the extraction as per standard care (if not already available).

At the time of surgery, local anesthesia will be administered. Conscious sedation will be administered according to patient need and investigator preference, per standard care. Buccal and lingual flaps will be minimally reflected to a point up to 3mm apical to

the bony crest. Prior to tooth extraction, the clinical measurement stent will be placed and measurements of ridge width and ridge height will be taken and recorded to the nearest 0.5mm. Ridge width will be measured to the nearest 0.5mm using a ridge caliper at a point **approximately 3mm apical to the facial and lingual bony crest** through small holes created in the stent at those locations. Ridge height will be measured to the nearest 0.5mm through two holes in the occlusal aspect of the stent – one hole directly above the facial bony crest and another hole directly above the lingual bony crest. This stent will be retained for use during the subsequent implant placement surgery.
Use of the stent and subsequent measurements are for research purposes, not standard care.

Tooth extraction will be performed as atraumatically as possible. Following tooth extraction, a final determination of enrollment into the study will be conducted based on the integrity of the buccal bone wall plate at the extraction site. If the buccal plate is intact, defined as **no bony dehiscence greater than 50% of the socket depth**, the patient will remain enrolled in the study. Conversely, if the buccal plate integrity has not been maintained (bony dehiscence >50%) the patient will be exited from the study and standard care therapy will be delivered to the patient.

After extraction, the number of bony walls in each socket will be recorded along with the presence of any bony dehiscences or fenestrations. Buccal and lingual flap elevation will be minimized and will extend no more than 2-3mm beyond the bony crest on the facial and lingual surfaces. The buccal plate thickness will be measured using an Iwanson gauge positioned perpendicular to the inner wall of the extraction socket. One beak of the gauge will be placed within the extraction socket 1.0mm apical to the alveolar bone crest. The other beak will be placed on the external bone surface 1.0mm apical to the alveolar bone crest. This buccal plate thickness measurement will be recorded to the nearest 0.1 mm. Measurements taken with the Iwanson gauge are for research purposes, not standard care.

The socket will be thoroughly debrided, the patient will be randomized to one of the study groups (Group 1, 2, 3 or 4), and the graft material will be placed in the extraction socket to a level even with the interproximal bone height of the mesial and distal aspects of the socket. The material will be condensed into the socket gently. In all sockets, a BioGide resorbable collagen membrane will be placed over the socket and graft material to retain the material in place. The edges of the membrane will be "tucked" under the flap margins to help with membrane retention, and the flaps will be sutured. Primary closure of the flaps will not be performed, per standard care. Flaps will be stabilized with chromic gut sutures, per standard care.

Visit 3 - Post-operative visit
The post-operative visit after extraction/ridge preservation will be scheduled approximately 3 weeks (±1 week) after the procedure. At this visit a clinic exam will be performed to evaluate healing. Any remaining sutures will be removed. If needed, an optional POT visit may be scheduled before this visit, per standard care and as determined by patient need.

Visit 4 - Pre-implantation:
Approximately 3-4 months after the extraction, the patient will be seen for pre-implant evaluation, per standard care. If needed, a cone beam computed tomography (CBCT) scan will be taken per standard care.
Prior to surgery, pregnancy status will be confirmed verbally. An over-the-counter pregnancy test will be provided if pregnancy status us unknown or suspected (research). A negative result is required to continue being in the study.

Visit 5 - Implant placement:
Prior to surgery, pregnancy status will be confirmed verbally. An over-the-counter pregnancy test will be provided if pregnancy status is unknown or suspected (research). A negative result is required to continue being in the study.

The implant surgery will be performed (standard care) at a time point 18 to 20 weeks after tooth extraction/ridge preservation (± 2 weeks). Per standard care, after local anesthesia (and conscious sedation if requested), the patient will undergo implant placement surgery at the previously extracted tooth site and if required simultaneous guided bone regeneration (GBR) will be performed as per standard care. First, the individual subject's measuring stent and caliper will be used to determine the ridge width and ridge height at the same locations as done in the tooth extraction/grafting surgery visit and all measurements will be documented for research purposes. During the implant bed preparation, a hollow drill will be used to allow retrieval of a bone core which will be collected and stored in formalin and subsequently examined histologically and outcomes including percentages of new bone formation, residual graft and connective tissue/other will be recorded. (Drilling procedure is per standard of care, collection of normally discarded bone core for analysis is a research procedure).
During the implant placement procedure, the following data will be recorded per standard care:

- Absence/Presence of bone defect, including dehiscence or crater like defect. If present, at what site(s) (Buccal, Mesial, Lingual, Distal) and what are the respective depth and width of these defects.

- Absence/Presence of bone fenestration. If present what is the size of the fenestration in height and width.
- Bone quality according Lekholm and Zarb (1985) classification
- Was additional bone grafting needed in case of thin bone or dehiscence of threads? Yes/No

Subject participation ends at the time of implant placement. However, standard care post-operative visits will be provided after implant placement. Generally, one or two post-operative visits will be provided during the first month after implant surgery to insure adequate healing.

6. Study Population

6.1. Study Population(s) Label/Name *To add more populations – select a row, copy & paste*	**6.2. Identify the criteria for <u>inclusion</u>** *The criteria that <u>every</u> potential participant must satisfy, to qualify for study entry.* All individuals in this study population must meet <u>all</u> of the inclusion criteria in order to be eligible to participate in the study	**6.3. Identify the criteria for <u>exclusion</u>** *The characteristics that make an individual ineligible for study participation.* All individuals in this study population meeting <u>any</u> of the exclusion criteria at baseline will be excluded from study participation.
Dental patients needing extraction of a non-molar ("single-rooted") tooth and ridge preservation	• English-speaking patients aged 18 to 90 • One tooth, excluding molars, that has been identified by dental faculty as requiring a single tooth extraction • A dental implant is indicated and treatment planned to replace the missing tooth • Have adequate restorative space for a dental implant-retained restoration • Have at least 10mm of alveolar bone height, without impinging on the maxillary sinus or inferior alveolar canal. • Have a dehiscence of the buccal or lingual bony plate of the tooth socket extending no more than 50% of the total depth of the socket. • Female patients who have undergone a hysterectomy, tubal ligation, or menopause, and non-pregnant women of child-bearing potential. • Are nonsmokers or former smokers. Current smokers may be included if they smoke <u>≤</u>10 cigarettes per day	• Will not cooperate with the follow-up schedule. • Patients will not be entered who are mentally incompetent, prisoners, or pregnant. • Pregnant women or women intending to become pregnant during the study period (as confirmed verbally; an over the counter pregnancy test will be provided if pregnancy status is unknown or suspected). • Patients who become pregnant during the study will be withdrawn and standard care will be delivered. • Smokers who smoke >10 cigarettes per day • Clinical and/or radiographic determinations which will preclude inclusion in this study are: Active infection other than periodontitis; Inadequate bone dimensions or restorative space for a dental implant; Presence of a disease entity, condition or therapeutic regimen which decreases probability of soft tissue and bony healing, e.g., poorly controlled diabetes, chemotherapeutic and immunosuppressive agents, autoimmune diseases, history of bisphosphonate use or long-term steroid therapy; Positive medical history of endocarditis following oral or dental surgery.

6.4. Will screen failures be allowed to <u>re-screen</u> at a later date?		**No**	X	**Yes**	*If yes, describe criteria below ↓*
	A patient who fails screening for a given tooth extraction may become eligible in the future should the patient require extraction of a different tooth				

7. Study Intervention(s) being tested or evaluated

This can include prevention, diagnostic or therapeutic interventions (e.g., drug or device) or educational, health services or basic science interventions (e.g., educational program, health care delivery model, or examining basic physiology)

Ridge preservation with one of 4 different materials (devices):
Group 1: DFDBA particulate at 125-850 micron size (Vallos)
Group 2: Xenograft (Bio-Oss) combined with DFDBA particulate at 125-850 micron size (Vallomix)
Group 3: DFDBA fibers (Vallos-F)
Group 4: Xenograft (Bio-Oss) combined with DFDBA fibers (Vallomix-F)

8. Protocol-Directed procedures, items, services or tests

List all procedures directed by the study plan - including items or services provided as part of routine or conventional care and those needed to diagnosis or treat research related complications.

Important Note – The protocol directed procedures listed must match those in the Schedule of Activities (attachment)

8.1. Drugs *(trade and generic, dosage, route of administration)*

N/A

8.2. Devices

Group 1: DFDBA particulate at 125-850 micron size (Vallos)
Group 2: Xenograft (Bio-Oss) combined with DFDBA particulate at 125-850 micron size (Vallomix)
Group 3: DFDBA fibers (Vallos-F)
Group 4: Xenograft (Bio-Oss) combined with DFDBA fibers (Vallomix-F)

8.3. Biologics

N/A

8.4. Laboratory Tests

- If needed: An over-the-counter urine pregnancy test will be provided to female subjects and self-administered in the graduate periodontics clinic of UTHSCSA. A negative result is required to enter the study.
- Histology of the core bone biopsy.

8.5. Imaging Procedures

N/A

8.6. Other Research Procedures *(e.g., other safety and efficacy assessments.)*

8.7 Attach a Schedule of Activities (SOA) Excel File [Download the Template here: *Schedule of Activities*] | *Check to indicate that the SOA Excel File is attached →*

9. Preparation/Handling/ Storage/Accountability of Investigational Drug, Biologic, or Device

N/A - This study does not include any investigational products (e.g. drugs, devices or biologics)

N/A - An Investigator Brochure is attached

N/A - A Drug/Device Manual is attached

9.1. Acquisition and accountability

State how the study intervention and control product will be provided to the investigator. Describe plans about how and by whom the study intervention will be distributed, including participation of a drug repository or pharmacy, and plans for disposal of expired or return of unused product.

All graft and membrane materials will be provided to the PI via standard shipping. Graft products are provided by Geistlich, Inc. in sterile single-use 1.0cc vials. All 25x25mm BioGide membranes are provided by Geistlich, Inc. in sterile single-use packaging. These materials are all commercially available.

9.2. Formulation, Appearance, Packaging, and Labeling

Describe the formulation, appearance, packaging, and labeling of the study intervention and control product, as supplied. Information in this section can usually be obtained from the IB or the package insert, or device labeling. This section should include the name of the manufacturer of the study intervention and control product.

9.3. Product Storage and Stability

Describe storage and stability requirements (e.g., protection from light, temperature, humidity) for the study intervention and control product. For studies in which multi-dose vials are utilized, provide additional information regarding stability and expiration time after initial use (e.g., the seal is broken).

All products can be stored at room temperature. There are no special storage requirements.

9.4. Preparation

Describe the preparation of the study intervention and control product, including any preparation required by study staff and/or study participants. Include thawing, diluting, mixing, and reconstitution/preparation instructions in this section. For devices, include any relevant assembly or use instructions.

Products are all used off-the-shelf.

10. Study Intervention Additional Details

10.1. Measures to Minimize Bias: Randomization and Blinding

This section should contain a description of randomization and blinding procedures (if applicable to the study design). It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that blinding or randomization might be compromised. Plans for the maintenance of trial randomization codes and appropriate blinding for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unblinding may occur and who may unblind. Provide the criteria for breaking the study blind or participant code. Discuss the circumstances in which the blind would be broken for an individual or for all participants (e.g., for serious adverse evets (SAEs)). Indicate to whom the intentional and unintentional breaking of the blind should be reported.

Randomization of subjects is done through use of envelopes inside which is a piece of paper with the group to which the subject will be assigned. 30 envelopes will be prepared for each of the 4 groups. The envelopes will be sealed and shuffled. The faculty staffing the procedure will draw an envelope from the stack prior to the surgical procedure appointment. Since the outcome of the study is the histologic healing, blinding of the surgeon is not necessary.

Blinding is performed only for histomorphometric measurements. The person doing histomorphometric analysis is blinded as to study group.

10.2. Study Intervention Compliance

Define how adherence to the protocol (e.g., administration of study intervention, use of device,) will be assessed, and verified (if applicable, e.g., plasma assays, electronic monitoring devices, daily diaries).

Patients will need to be present at each scheduled visit. Failure to attend visits will result in exit from the study. All providers placing study materials as part of the study intervention will be trained and provided with detailed instructions to ensure methods are consistent and in compliance with the protocol. All faculty staffing residents are familiar with the study protocol and can verify the results of the procedure and measurements taken.

10.3. Permitted Concomitant Therapy

This section should be consistent with the medication restrictions in the inclusion/exclusion criteria previously listed. Describe how allowed concomitant therapy might affect the outcome (e.g., drug-drug interaction, direct effects on the study endpoints).

N/A

10.4. Rescue Medicine

List all medications, treatments, and/or procedures that may be provided during the study for "rescue therapy" and relevant instructions.

N/A, no rescue medicine

11. Study Intervention Discontinuation

11.1. Discontinuation of Study Intervention

Describe the criteria for discontinuing the study intervention (e.g., halting rules), including any monitoring test(s) and associated clinical decision point(s). Include reasons for temporary discontinuation of the study intervention (e.g., type and quantity of adverse events), clearly stating the length of time, if applicable, and describe the data to be collected at the time of study intervention discontinuation and approaches for restarting administration of or re-challenging with study intervention.

Study will be discontinued if more than 5% of subjects present an adverse reaction such as infection or material recall. Such a reaction would be extremely rare as the study materials are FDA approved have been on use in the US market for years.

11.2. Continued Follow-up Discontinuation of Study Intervention

Describe efforts that will be made to continue follow-up of participants who discontinue the study intervention, but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Reasonable efforts must be made to undertake protocol-specified safety follow-up procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems involving risks to subjects or others (UPIRSOs).

All patients that participate in the study, including those discontinued due to adverse reactions, will be followed until completion of the study or resolution of the adverse reaction (unless consent has been withdrawn).

12. Statistical Considerations

12.1. Statistical Hypotheses

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

Null hypothesis: a) No difference in % vital bone, % residual graft and % connective /other tissues between the groups.
b) No dimensional differences in alveolar ridge after ridge preservation between the groups.

12.2. Sample Size Determination

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants.

Using ANOVA, power analysis determined that we will be powered to find an overall difference among groups with 90% power if we enroll N=16/group (N=64) total. To account for attrition of 20%, an N=20 per group is needed. For post-hoc tests, this sample size will enable us to identify a difference of 15% bone (SD:15) between each of the groups 2-4 as compared to DFDBA particulate (group 1; control) with greater than 80% power. Because we also plan to do pairwise comparisons between groups, a larger N is desired. Thus, we will enroll 30 subjects per treatment group (120 total).

12.3. Populations for Analyses

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each).

All study participants who complete the study intervention will be included in the analysis for all outcome measures.

12.4. Statistical Analyses

Include analysis of primary efficacy endpoints, secondary endpoints, safety analyses, and any planned interim analyses

The outcomes of the histologic and clinical parameters will be summarized with the sample size, mean, standard deviation, median, minimum and maximum. ANOVA will be used to determine differences between the 4 groups. Post-hoc tests will be performed to determine differences between the DFDBA particulate group (Group 1 – active control) and the other 3 groups. Pairwaise comparisons between groups will be assessed with two-sample *t*-testing. The significance of variation in the group effect with another variable will be assessed with an interaction term in a linear model. All statistical testing will be two-sided with a significance level of 5%. Spearman rank and Pearson correlations between clinical parameters and histologic parameters will be analyzed as well. All statistical analyses will be done with statistical software.