Document Coversheet

Study Title: Bone Quality and Quantity in the Maxillary Sinus Grafted With Xenograft or Synthetic Bone Substitute: A Radiographic and Histomorphometric Randomized Controlled Clinical Study

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	9/7/2023
NCT Number:	NCT04433117
IRB Number	58349
Coversheet created:	2/7/2024

PROTOCOL TYPE (VERSION 4)

IRB Approval
9/7/2023
IRB # 58349
IRB1
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Which IRB

- (•) Medical ( ) NonMedical

Protocol Process Type

- ( ) Exemption
- ( ) Expedited (Must be risk level 1)
- (•) Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

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PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Bone Quality and Quantity in the Maxillary Sinus Grafted with Xenograft or Synthetic Bone Substitute: A Radiographic and Histomorphometric Randomized Controlled Clinical Study

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

Bone Quality and Quantity Maxillary Sinus Graft

Anticipated Ending Date of Research Project: 6/1/2023

Maximum number of human subjects (or records/specimens to be reviewed) 30

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? (•) Yes ( ) No

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SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc.) 20 to 27

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

Subjects who seek to replace missing maxillary teeth with dental implants and have pneumatized maxillary sinuses will be voluntarily recruited from University of Kentucky College of Dentistry clinics. Eligible subjects will be randomly assigned into one of two treatment groups; the test group (n=10) will receive ShefaBone? synthetic material and control group (n=10) will receive Bio-Oss? xenograft material.
Inclusion and Exclusion Criteria:
Subjects have to be 20 to 75 years of age and have at least one maxillary edentulous posterior site requiring maxillary sinus grafting and replacement with a dental implant. Subjects will be excluded from this study if they are current smokers/use tobacco, are pregnant, have active periodontal disease, uncontrolled diabetes, any autoimmune disease, kidney disease, or liver disease or receiving radiation or chemotherapy. Finally, subjects will also be excluded if they have any type of radiographic periapical pathology such as a periapical abscess.

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:				
Black/African American:				
Latinx:				
Native Hawaiian/Pacific Islander:				
White:				
American Arab/Middle Eastern/North African:				
Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why:

There will be no restriction for
race or ethnicity. Any subject that
presents fitting the criteria specified in the inclusion section could
participate in the study.

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on

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the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☑ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

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Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

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INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF.**
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Attach Type	File Name
Informed Consent/HIPAA Combined Form	58349 Kudsi Consent.pdf

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)
- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

The research study will be conducted at the facilities of the University of Kentucky, College of Dentistry after approval by the Institutional Review Board. All members of the research team received training in human subject protection. After each patient has been given verbal and written information describing the nature of the study, informed consent will be obtained before he or she can enter the study. A copy of the consent form will be given to the patient and another retained by the investigator. Patients will not be screened until an informed consent has been obtained.
Subject complaints will be addressed to PI. The PI will personally address complaints with the intent to resolve any concerns that may arise. If the patient requests to be removed from the study their request will be granted at no detriment to the study participant. Subjects with questions or complaints about their rights as a research participant will be advised to contact the Office of Research Integrity.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

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e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the
not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

☐ Request for Waiver of Signatures

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If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the ***Cover Letter Template*** *as a guide. There is an English and a Spanish version.*

○ **Option 1**

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

○ **Option 2**

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

○ **Option 3**

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Hard and soft tissue deficiencies of an alveolar ridge arise as sequelae of tooth extraction when socket preservation is not applied (Sharan and Madjar 2008). In addition, extraction of posterior maxillary teeth causes pneumatization of the maxillary sinus in relation to other fixed landmarks such as the teeth. These anatomic sinus limitations and alveolar bone deficiencies are the main challenges for dental implant placement. Different bone substitutes have been used to augment bone in pneumatized maxillary sinuses. (Bielecki and M Dohan Ehrenfest 2012; Ribeiro et al. 2012; Zhang 2011).

The use of fresh autogenous bone has been considered the gold standard when grafting the maxillary sinus (Bertolai et al. 2015). However, morbidity of the donor site and a limited volume of available bone are disadvantageous to such a procedure. Scaffolding materials such as xenografts or synthetics substitutes have been proven to be a viable alternative (Butz and Huys 2005; Zitzmann et al. 2001).

Xenografts are obtained from nonhuman species and serve as a scaffold for the formation of new bone (osteoconduction). Histologic evaluation of maxillary sinuses grafted with xenografts revealed newly formed bone to be mostly woven bone with some remodeling to lamellar bone. These histologic findings reaffirm the osteoconductive ability of xenografts when used as the sole grafting material in maxillary sinus augmentation (Testori et al. 2013). Xenografts appear to be an effective method for maxillary sinus grafting and demonstrate limited resorption over time (Galindo-Moreno et al. 2013).

Sinuses augmented with synthetic bone substitute (SBS) also appear to successfully integrate based on recent histomorphometric studies. (La Monaca et al. 2018) demonstrated vascularization and trabecular bone formation in sinuses grafted with SBS. One type of SBS includes porous granules of bioactive and resorbable silica-calcium phosphate nanocomposite (ShefaBone?). ShefaBone? grafts offer a novel alternative that can potentially unite the 3 salient bone-forming properties (osteoinduction, osteoconduction, and osteogenesis).
ShefaBone? has unique properties including: 1) bioactivity 2) bioresorbablility, and 3) allowing for the uptake of calcium ions from the physiological solution and releasing phosphate and silicate ions which aid in bone formation (Al-Fotawi et al. 2019). A material with such properties will substitute bone in a more controlled and effective combination that can be obtained in many clinical situations, without the disadvantages found with autograft (Al-Sabbagh et al. 2013). ShefaBone? has demonstrated successful regenerative properties for bony defects (Al-Fotawi et al. 2019).
To our knowledge, there is no reported clinical studies on the use of SCPC material to graft a pneumatized maxillary sinus. This aim of this current study is to compare SCPC to commonly used xenograft material in an augmented maxillary sinus.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

1. To assess the quality and quantity of the maxillary sinus bone prior to the placement of dental implants and subsequent restorations, approximately 20 patients will be randomly assigned to receive an augmentation of the maxillary sinus region using either Shefabone (synthetic bone) or Bio-Oss (xenograft).

2. With the use of pre-operative and post-operative limited view CBCT radiography, the maxillary sinus bone density will be assessed and compared between the individuals receiving Shefabone and the individuals receiving xenograft material.

3. Histomorphometric analysis will be used to assess, compare and contrast the quality and the quantity of the new vital bone cells generated when using these different graft materials.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.

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- *Community-Based Participatory Research*: If you are conducting community-based participatory research (C strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

The current study will be a single site, randomized, controlled clinical and histological investigation. Subject recruitment: May 2020 - January 2022 with 20 subjects, there will be no placebo medication at any point in the research procedures.
Eligible patients will be randomly assigned to one of two treatment groups using a randomization table generated by a computer. The test group (10 sinuses) will receive Shefabone and control group (10 sinuses) will receive Bio-Oss xenograft material. Little is known about the distribution of bone quality changes in patients who receive Shefabone graft to augment the maxillary sinus. Ten subjects per group is reasonable to providing an 80% probability of estimating the true mean for bone quality and implant stability to within half a standard deviation in each group.

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

The PI will recruit subjects from the University of Kentucky College of Dentistry clinics. Subjects that are coming for treatment of missing maxillary teeth and have a pneumatized maxillary sinus, and match the inclusion criteria will be told about the research and offered the opportunity to participate. Only the PI outlined in this IRB application will select study participants. Selection will be inclusive of patients who give signed permission to participate.
The population's data will be identified and only the PI will have secured access to that data. The participant will be interacting with the investigator only; this will be done chairside within the UKCD periodontics clinic only.
No advertisement will be used at this time.

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

All patients who agree to take part in this study will be placed in a randomization table to determine which product they will receive and which clinician will be performing the surgery. Therefore, no one clinician will be performing the entire test or all of the control groups; it will be completely randomized.

Visit 1:

Subjects will be asked to read and sign the Informed Consent as well as encouraged to ask any questions related to the study. Subjects will sign the Informed Consent form and receive a copy of their consent. Subjects will be enrolled if they meet the inclusion criteria and none of the exclusion criteria. An oral tissue examination then been performed and a limited view CBCT scan will be taken of the maxillary arch.
Subjects will be randomly assigned in the control and test group using a computer generated randomization table. Subjects who have compromised health, due to any of the exclusion criteria, which may affect the ability of the subject's tissues to heal, will be excluded from the study.

Visit 2:

After administration of a local anesthesia (Lidocaine 2% injection with 1:100,000 Epinephrine), a cresto-palatal incision will be performed using a 15C surgical blade at the maxillary posterior edentulous site. Full thickness muco-periosteal flap will be reflected with a vertical releasing incisions. The osteotomy will be prepared on the lateral wall of maxillary sinus area using the Piezosurgery unit. A lateral window will be open to completely reflect the Schneiderian membrane and 2 grams of the ShefaBone? (porous granules of bioactive and resorbable silica-calcium phosphate nanocomposite), graft material will be applied into the sinus site for test group and 2 grams of Bio-Oss? (bovine bone in a validated multistage purification process to remove the organic components), for control group. The grafted site will be covered with a resorbable collagen membrane to perform guided bone regeneration (GBR) and to protect the bone graft from the intrusion of undesired soft tissue growth. The flap will be secured using an interrupted suture with tension free primary closure. A second limited view CBCT will be taken as standard of care. After surgery, subjects will be given post-operative instructions.

Augmentin 875/125 mg, one tablet every 12 hours for 10 days will be prescribed. This recommendation of antibiotics will be given to each subject based on current UK College of Dentistry implant protocol and started one day before the surgery. For subjects unable to take amoxicillin for any reason, an alternative antibiotic will be prescribed, i.e. Z-PAK (Zithromax) 250mg (5 day PAK) Take 2 tablets on day one, then 1 tablet daily on days 2 through 5. Analgesic, Ibuprofen up to 600 mg every 6 hours will be prescribed as needed. Subjects will be advised to clean the surgical area gently with a Toothette® Oral Swab moistened with 0.12% chlorhexidine gluconate four times daily for two weeks.

Visit 3:

Subjects will return in two weeks after the surgical visit to have the sutures removed and for evaluation of healing.

Visit 4:

Subjects will return five months following the first surgical visit to have their second CBCT completed. This second CBCT will allow for planning of the implant placement.

Visit 5:

Subjects will return five months after the surgical visit when healing of the bone grafting will be achieved. After local anesthesia administration, (Lidocaine 2% injection with 1: 100,000 epinephrine), cresto-palatal incision will be made and full thickness flap will be reflected. Osteotomy will be prepared in the anterior and posterior of the lateral window of the grafted site using a 3 mm (outside diameter), 2 mm (inside diameter) trephine bur with irrigation at a speed of 1000 rpm based on 3D printed template. Core samples, 5 mm in length and 2 mm in diameter, of newly regenerated bone will be retrieved from the center of the grafted lateral window, where the bone healing will be considered least mature. Harvested core samples will be of such size as not to compromise same appointment implant placement in the grafted site. Osteotomy core sites will be grafted using conventional bone graft. Core samples will be placed immediately in formalin. A dental implant/s will be placed after a complete osteotomy will be achieved according to

implant manufacturer recommendations.
Cover screws will be placed, and flaps will be secured with (4-0") resorbable sutures. Subjects will be given postoperative care as well as home care instructions. Subjects will be advised to clean the surgical area gently with a Toothette® Oral Swab moistened with 0.12% chlorhexidine gluconate four times daily for two weeks.

Research vs. Standard of Care in the Surgical Steps (Visit 2 and Visit 5):

Visit 2
1. Administration of anesthetic and reflection of full thickness flap. –Standard of Care.
2. Maxillary sinus lateral wall osteotomy made with Piezosurgery unit. –Standard of Care.
3. Administration of graft material. –Research Procedure.
4. Covering window with a membrane and suturing flap closed with primary closure. –Standard of Care.

Visit 5
1. Administration of anesthetic and reflection of full thickness flap. –Standard of Care.
2. Harvesting of bone core sample from graft site. –Research Procedure.
3. Placing implant/s and cover screws with primary stability. –Standard of Care.
4. Suturing flap closed with primary closure. –Standard of Care.

Visit 6
1. Return 2 weeks after implant placement to evaluate soft tissue healing.

Please find the attached file illustrating the number of visits.

Attachments

Attach Type	File Name
ResearchProcedures	Visit diagram.docx
ResearchProcedures	Visit diagram.docx

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Clinical:
The treatment will be considered successful if the bone core samples can be retrieved and sufficient bone will be present for implants to be placed after five months of healing. Failure of treatment will be considered when the bone core samples will not be harvested or implant placement will not be performed at five months of healing. Any failure will be treated as conventional treatment protocol followed at UKCD without further cost to subjects.

Radiographic:
Limited view CBCT scan will be taken at baseline before sinus augmentation procedure as standard of care and after sinus augmentation and again at five months prior to implant placement as standard of care. The radiographs will be analyzed by a blinded investigator. The bone width and height will be measured preoperative and postoperative of the grafted site. Proposed area for the lateral window osteotomy will be outlined on limited view CBCT scan which is more accurate and less than the conventional CBCT. Two sagittal sections on the CBCT scan will be detected. One at the anterior part of the outlined window and the other one at the posterior part of the outlined window. These two sagittal sections will be used in the sinus measurement analysis. On each sagittal section of the CBCT scan, two lines will be drawn to measure the dimensions of the sinus. One line will measure the horizontal width and the other line will measure the vertical height. The horizontal width will be measured at a vertical height of 10 mm from the sinus floor in the sinus cavity based on the conventional average length of dental implant used in implant dentistry. The difference in the measurements for all surgical sites after the grafting procedure and before the implant placement will provide a clinical assessment of the amount of bone regeneration.
The radiation dose from a typical CBCT is about 1/40th of the typical natural background radiation dose that we all receive every year. It is also about 1/7th of the annual safe dose limit (not including medical exposures) for members of the public and well below the levels that are considered a significant risk of any harmful effects. The radiation dose from a typical dental x-ray is about 1/80th of the typical natural background radiation dose that we all receive every year. It is also about 1/7th of the annual safe dose limit (not including medical exposures) for members of the public and well below the levels that are considered a significant risk of any harmful effects.

Histomorphometric:
Twenty trephined core samples will be retrieved surgically from the grafted lateral window at the time of implant placement (Visit 5). One core sample will be retrieved from the center of the grafted site.
Core samples will be placed in special biopsy tubes containing 10% neutral buffered formalin for fixation at least 24 hours prior to decalcification in Decal Stat™ acid for one hour, dehydrated in a graded series of Ethanol, and embedded in Ameraffin tissue

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embedding medium wax. Harvested core samples will be sent to a research laboratory for light microscopy histol preparation. The specimens will be cut in the apico-coronal plane to obtain three -6µm – thick sections and then will be stained with hematoxylin and eosin. For each biopsy specimen, 6 to 9 longitudinal sections will be used for light microscopic examination. Histomorphometric analysis will be performed on three fields for each section using specialized software (ImageJ, http://rsbweb.nih.gov/ij/). Volume of vital bone, graft remnants, and connective tissue will be measured based on the averages of the percentages at a magnification of 63X. Data will be statistically analyzed using Statistical Package for the Social Sciences (SPSS 13.0 for Windows software) program to compare between test and control groups.

Photographic:
For each visit, photographs will be taken using a digital camera for step-by-step documentation and monitoring of the healing process. Documenting each case through photographs is the standard of care in the Graduate Periodontology Clinic and no measurements will be taken using the photographs.

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Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

Research activities will be conducted at the University of Kentucky, College of Dentistry research facilities.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Any surgical procedure, including bone grafting and implant placement, would involve risks such as bleeding, infection, inflammation, and pain. In addition to that, bone graft placement may result in sinus membrane perforation, nerve injury, graft reabsorption, and graft rejection. No one will guarantee patients that this procedure will have certain results. There is always a chance that any medical treatment can harm, and the investigational treatment in this study is no different. In addition to the risks listed below, you may experience a previously unknown risk or side effect.

The risks associated with this study are those normally encountered when receiving dental care in a private practice setting. However, if patients experience pain that cannot be managed by the prescribed analgesic, they will be told to contact the principal investigator for follow-up. Risk after surgery include swelling, bruising, mild to moderate pain. Infection is unlikely, However, if an infection arises, subjects will be treated with a course of antibiotics. Subjects will be monitored for other adverse reactions throughout the study. All adverse events will be managed and documented by the principal investigator. The emergency team of the College of Dentistry or the College of Medicine is available for immediate support in case of emergency. Oxygen, glucose drinks and temporary emergency measures are available in the Clinical Research Center.
Some patients refuse to use animal bone or human bone - the synthetic bone substitute tested in this study will provide society an alternative treatment to restore bone and eventually missing dentition.
The patient will be informed that participation in the study is voluntary and that he/she may withdraw at any time without any loss of benefits.

Available Alternative Opportunities/Treatments

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Describe alternative treatments or opportunities that might be available to those who choose not to participate in the offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

This research is a prospective study. If the patient does not want to be in the study, he/she does not have to participate.

Subjects will be informed of clinical findings and treatment options, whether or not those options are part of the study. Subjects are free to pursue other treatment options not included in this study at their own expense. Current treatment for pneumatized sinus includes maxillary sinus augmentation utilizing the lateral window technique and implant placement to restore the function of mastication.

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

All source documents for potential subjects including medical/dental histories, demographic data, consent forms, treatment notes and study data will be stored in a locked cabinet in a locked room (D-432). All documents will be identified by a study number. There will be minimal to no possibility of incidental findings. Only the principal investigator will have access to all the data and patient identifiers. And all subjects identifiers will be removed prior to sending essential data to the statistician for analysis, only the principal investigator will have the master list of subjects and their demographic data.

We will make every effort to keep private all research records that identify you to the extent allowed by law. Subject's information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. Subjects will not be personally identified in these written materials. We may publish the results of this study; however, we will keep subject's name and other identifying information private.
Data will be collected and stored by PI on a University of Kentucky secured server as a password protected files. Only electronic devices behind the university firewall, which encrypt all personal health information or other identifying information will be used.
Research materials in hard copy form will be kept in locked file cabinets and in a locked room (D-432). Data will not be shared with persons outside those approved in this IRB. Only IRB approved researchers will be able to request access to identified data. Signed documents (e.g., signed consents/assents) and IRB records will be stored in locked file cabinets and in locked offices for at least six years after study closure.
All treatment will be conducted under Universal Precautions and as a standard of care.

Analgesic will be prescribed to minimize post-operative pain (600 mg ibuprofen three times per day). Antibiotic regimen will be prescribed to minimize the likelihood of developing an infection during the healing period. Icepack will be recommended to minimize swelling.
All data collected will be stored in a password-protected computer that is stored in a locked room in the Division of Periodontology, College of Dentistry, University of Kentucky

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?

◉ Yes ○ No

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered,

indicate the amount and describe the terms and schedule of payment. Please review this guidance for more inform
subjects, including restrictions and expectations.

Subjects will receive the following amount to compensate for their time in each follow-up visit:
• Visit 1: 30-45 minutes; $50 gift card.
• Visit 2: 60-90 minutes; $50 gift card.
• Visit 3: 30-45 minutes; $50 gift card.
• Visit 4: 30-45 minutes; $50 gift card.
• Visit 5: 60-90 minutes; $50 gift card.
• Visit 6: 30-45 minutes; $50 gift card.
You will receive a total of $300 gift card at the end of your sixth visit at our clinic.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

Subjects will not be responsible for any research only procedure and will be responsible for the standard of care procedures.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

Data will be reviewed weekly with Dr. Al-Sabbagh, all data collection will be done by Dr. Kudsi and all surgical protocol will be as per standard Graduate Periodontology Surgical protocol.

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Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the information or samples collected in this study. This means that no link or code to your identity will be kept. After all identifiers have been removed, the information or samples may be used for future research or shared with other researchers without your additional informed consent. Once you give your permission to have your de-identified information or samples stored, they will be available indefinitely and cannot be removed due to the inability to identify them.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

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Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

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Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis**
○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?
○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

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HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form
☐ HIPAA Waiver of Authorization

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STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

○ Yes ◉ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ○ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any

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applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA co
etc.) should be attached using "Other Drug Documentation" for the document type.

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STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

◉ Yes ○ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer "no" above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

21 CFR 807

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ◉ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor's authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

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Does the intended use of any research device being tested (not clinically observed) in this study meet the regul
Significant Risk (SR) device?

- ○ Yes. Device(s) being tested in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- ◉ No. All devices being tested in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

Attach Type	File Name
Study Device Form	Study Device Form 04 21 2020 - 1.pdf
Study Device Form	Study Device Form 04 21 2020 - 2.pdf

Statistical Analysis

For bone radiographic bone height analysis, ten subjects per group will provide 80% power to detect an effect size of 1.4 on newly formed bone using an independent two group t-test with a 5% two-sided significance level. An exploratory analysis was carried out to verify the normality supposition by Shapiro-Wilk. Non-parametric distribution was observed for the variables of bone and new bone percentage measurements; however, biomaterial data was classified with a Gaussian distribution. Thus, Mann-Whitney and T-test were applied for intergroup comparisons, respectively. Fisher Exact Test was performed between treatment groups. $P \leq 0.05$ was considered significant. Sigma Plot software was used for statistical analysis.