A RANDOMIZED, SPLIT MOUTH STUDY OF THE EFFECTS OF BONE GRAFT PARTICLE SIZE ON BONE VITALITY AND BONE VOLUME OUTCOMES IN SUBJECTS UNDERGOING SINUS AUGMENTATION FOR THE PLACEMENT OF DENTAL IMPLANTS

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Study Product: PUROS™

Protocol Number: 19-00996

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Study Number:	19-00996
Funding Sponsor:	Zimmer-Biomet
Study Product:	Puros allograft
Study Product Provider:	Zimmer-Biomet

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CRF	Case Report Form
DCC	Data Coordinating Center
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
EHR	Electronic Health Record
FDA	Food and Drug Administration
ML	Marginal Bone Loss
NYUCD	New York University, College of Dentistry
CBCT	Cone Beam Computed Tomography
CT	Computed Tomography
PA	Peri-apical radiographs
SD	Standard Deviation
IQR	The Interquartile Range

Protocol Summary

Title	A RANDOMIZED, SPLIT MOUTH STUDY OF THE EFFECTS OF BONE GRAFT PARTICLE SIZE ON BONE VITALITY AND BONE VOLUME OUTCOMES IN SUBJECTS UNDERGOING SINUS AUGMENTATION FOR THE PLACEMENT OF DENTAL IMPLANTS
Short Title	Bone graft particle size on bone vitality and volume.
Brief Summary	This is a randomized, split mouth study. Up to 10 subjects who will receive the sinus augmentation surgery on both sides will be included in this study.
Objectives.	The purpose of this study is to evaluate the influence of bone allograft particle size on bone vitality and bone volume in subjects undergoing sinus augmentation for the placement of dental implants.
Methodology	Randomized, split mouth
Study Duration	42 months
Participant Duration	24 months
Population	10 subjects, male or female, healthy
Study Sites	NYU College of Dentistry- clinic 5 W
Number of participants	10 participants expected to be enrolled

Study Summary

Title	A RANDOMIZED, SPLIT MOUTH STUDY OF THE EFFECTS OF BONE GRAFT PARTICLE SIZE ON BONE VITALITY AND BONE VOLUME OUTCOMES IN SUBJECTS UNDERGOING SINUS AUGMENTATION FOR THE PLACEMENT OF DENTAL IMPLANTS
Short Title	Bone graft particle size on bone vitality and volume
Protocol Number	19-00996
Phase	Phase 2
Methodology	Randomized, single-masked, split-mouth, single center study
Study Duration	3.5 years
Study Center(s)	Single-center
Objectives	To determine the effects of small and large bone graft particles vs large particles alone on percent vital bone, percent residual graft material, measured histologically from bone biopsies of the grafted site taken at the time of dental implant placement from subjects undergoing sinus augmentation for the placement of dental implants. Dental radiographs taken post operatively will be used to estimate bone graft volume differences between conditions.
Number of Subjects	10
Diagnosis and Main Inclusion Criteria	Subjects have missing upper back teeth on both the left and right sides and insufficient bone height (<5mm) for dental implant placement
Study Product, Dose, Route, Regimen	Bone graft material will consist of four to six grams of commercially available human donor bone allograft (Puros Allograft Bone Particles, Zimmer Biomet, Warsaw, IN USA) consisting of cortical and cancellous bone chips of either 250-1000 microns, and 1000-2000 microns size, vs. 1000-2000 microns size alone.
Duration of administration	Bone graft material is implanted, dental implants are placed, restored and subjects are followed for a period of two years after implants are restored
Statistical Methodology	Two test site bone biopsies will be compared with regard to microscopic measures of percent vital bone and residual graft material. The average of three histological specimens for each test sites of the subject biopsy will be calculated. Mean percent vital bone and percent residual graft material and standard deviations for each condition will be calculated. Condition comparisons will be made by two-sided paired t-test. Sample size assumptions: Previous studies indicate that a sample size of 10 subjects will have 80% power to detect a 25-50% difference in percent vital bone and 100% in residual graft material with 95% confidence.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

1.1 Background

Tooth loss due to dental caries, and periodontal disease is a major cause of chewing dysfunction among adults in the United States. Dental implants have been approved for use in the United States for tooth replacement since 1983. Root form dental implants are made of titanium or titanium alloy that allows for the phenomena called osseointegration to occur. Osseointegration is the biological process by which bone cells adhere and grow onto the root form titanium implant. The process of osseointegration takes from 4-8 weeks, after which a dental prosthesis can be placed on the implants. This prosthesis can be a crown, or a bridge, or a denture. Dental implants can be placed anywhere in the mouth where teeth were formerly present, however the quality and quantity of jaw bone determines whether a dental implant may be placed.

The upper jaw can be a challenging area for implant placement. The upper jaw bone or maxilla, is generally less dense than other part of the mouth. Further, after tooth loss, the upper jaw undergoes a process called residual ridge resorption, that is, in the absence of teeth, mechanical load on the jaw is lessened, and bone atrophy occurs. Concurrently, the maxillary sinus, which is adjacent to the upper jaw bone, undergoes a process call pneumatization, whereby the sinus space increases, and the amount of maxillary jaw bone present diminishes. The amount of bone loss due to these processes is variable. When the amount of available jaw bone in the maxilla is less than 6 millimeters, (the length of the shortest commercially available dental implant) the placement of dental implants is not feasible without bone augmentation.

The sinus augmentation procedure was developed by clinicians in order to increase the amount of bone for the placement of dental implants. The sinus augmentation, or 'sinus lift' is a chairside dental surgery procedure, whereby a window is surgically created in the upper jaw near the sinus, the delicate sinus membrane is elevated, and bone substitute material is placed into the sinus. The gingiva and oral mucosa are then sutured and the sinus is allowed to heal for a period of about six months. The bone substitute material that is used in the sinus augmentation has varied considerably, and while many different bone substitute materials perform adequately, the ideal bone substitute composition has to date not been defined. Previous studies have examined the amount of new bone formation, and the amount of residual graft material from core biopsies taken after the sinus augmentation period were examined histologically (under the microscope). Classical studies have shown that normal human maxillary jaw bone is comprised of approximately 40% bone and 60% other tissues. To date the best results obtained by using human donor bone allograft, have resulted in 25% bone formation and 75% other tissues. The size and source of the allograft materials has been controversial. Cortical bone is the thicker denser outer bone, such as is found at the surface of the jaw, while cancellous bone is the more porous, spongier bone found within the jaw. The particle size of these two bone graft types is also important, particle size is important for the attraction of new bone cells into the graft, but also to provide a scaffold for the maintenance of volume of the bone graft. Clinicians have traditionally chosen larger bone graft particle size in the belief that they provide a more durable scaffold thus ensuring maintenance of the bone graft volume. It has previously been demonstrated that the large particle sizes perform adequately, for dental implants, but our early results suggest that by adding smaller particle sizes to the bone graft mix, a higher proportion of new bone may be obtained without loss of graft volume. The ultimate goal would be to define the type and particle size that is optimal for new bone formation that is the same or greater density as native bone.

The purpose of this study therefore is to compare the new bone formation and bone graft volume between bone graft mixes comparing two different size graft particles and follow the survival of the dental implants up to two years after prosthetic loading.

1.2 STUDY DEVICE

Bone graft material will consist of four to six grams of commercially available human donor bone allograft (Puros Allograft Bone Particles, Zimmer Biomet, Warsaw, IN USA) consisting of cortical and cancellous

bone chips of both 250-1000 microns, and 1000-2000 microns size, or 1000-2000 microns size alone. The method and composition of these products has been described, both products are FDA approved and commercially available. The harvesting and processing of the graft materials is briefly described as follows:

Puros Allograft Bone Particles are sterile, dehydrated cortical and/or bone from donated human tissue with the Tutoplast® Process. The donated human tissue utilized for this implant was recovered from a donor screened for risk factors associated with infectious diseases and medical conditions that rule out donation. The donor's blood was tested for relevant communicable diseases in a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) or equivalent and registered with the U.S. Food and Drug Admiration (FDA) for donor testing. The following test criteria were met for this donor:

REQUIRED INFECTIOUS DISEASE TESTING BLOOD TEST ACCEPTABLE RESULT
- HIV-1 / HIV-2 Antibody Negative/ Non-Reactive
- Hepatitis C Virus Antibody Negative/ Non-Reactive
- Hepatitis B Surface Antigen Negative/ Non-Reactive
- Hepatitis B Core Antibody (Total) Negative/ Non-Reactive
- Syphilis Negative/ Non-Reactive
- Human T-Cell Lymphotropic Virus I/II Antibody Negative/ Non-Reactive
- HIV-1 NAT-TMA Negative/ Non-Reactive
- HCV NAT-TMA Negative/ Non-Reactive

Tutoplast® Process, a proprietary tissue graft cleaning and preservation process using solvent dehydration that virtually eliminates the possibility of disease transmission, without compromising its biological or mechanical properties. It has been commercially available for more than 30 years and utilized in all surgical disciplines, including dentistry, gynecology, neurosurgery, ophthalmology, orthopedics, otolaryngology, pediatric and urology surgery. More than 1.5 million implants have been safely and effectively implanted without a single documented case of disease transmission. This is because the Tutoplast process addresses all pertinent issues of tissue grafting and implantation. In addition, RTI Biologics (former Tutogen Medical, Inc.) meets or exceeds all requirements set by the Food and Drug Administration (FDA) and American Association of Tissue Banks (AATB). The Tutoplast process has been validated through numerous independent laboratory studies.

A licensed physician for RTI Biologics Inc. determined that the donor met eligibility requirements. The physician utilized available relevant information which may have included, but was not limited to: family/next-of-kin interview, medical/hospital records, do- nor physical assessment, infectious disease test results, radiology/pathology reports, death certificate and autopsy report (if performed). Puros Allograft Bone Particles and the CopiOs Pericardium membrane are preserved by the Tutoplast® process which maintains the collagen matrix of native bone and undergoes 5 stages of: i. Delipidization, ii. Osmotic treatment, iii. Oxidative treatment, iv. Solvent dehydration, and v. Low dose gamma radiation is applied terminally to the product to achieve a sterility assurance level (SAL) of 10^{-6}.

1.3 Clinical Data to Date

Sinus augmentation using a lateral window technique was first described by Boyne and James[1] and Tatum.[2] One aim of this procedure is to obtain a volume of bone sufficient for the mechanical support and integration of dental implants.[3] Various grafting materials have been used such as autogenous bone (harvesting bone from another part of the patient, such as the hip), allografts (processed human donor bone), xenografts(processed animal bone), alloplastic materials (Silicate or calcium sulphate), and a combination of these materials.[4-6] There are disadvantages to the use of autogenous grafts which include morbidity because of the need for two surgical sites and the need to perform this procedure in a hospital setting. Allografts and xenografts are commercially available and commonly used for lateral window sinus augmentations due to their lower cost, no need for hospitalization, and predictability of clinical outcome. Using these materials has been shown to form sufficient bone quality for the osseointegration of implants and acceptance of their load bearing potential.[7-9]

Mineralized cortical and/or cancellous bone allografts are used as bone replacement grafts for orthopedic and dental applications, and have been extensively used for sinus augmentation[10-12], but the optimum size of the graft particles has not been defined.

1.4 Treatment Planning

In this study, we will use cancellous and cortical allograft in a 50-50 ratio, and compare graft particle sizes. Due to their porous architecture, cancellous particles promote vessel penetration, allowing osteogenic cell movement and rapid re-vascularization. They also contain a lower density mineral component and higher collagen content, thus promoting quicker turnover. Since their high turnover rate can lead to significant volume loss, cortical particles, which are denser, are added to preserve the intended volume of the graft and to reduce shrinkage. The structural integrity of the cortical particles, the high mineral and low collagen contents, and their reduced turnover rate allow for space-maintenance, leading to decreased volume loss[13]. Using two different sizes of cancellous and cortical allograft will allow for comparison of histological and clinical outcomes, and help to define the optimal particle size graft material.

1.5 Research Risks & Benefits

The products used in the present study are FDA approved for this purpose, and have well documented safety profiles, therefore we anticipate minimal risk to study subjects due to the graft materials used. Both sizes of graft material are used for sinus augmentation procedures at the discretion of dentists, outside of this study. To date there are no specific guidelines as to which particle size is more favorable and therefore should be exclusively used for the sinus augmentation procedures. The risks associated with randomization are one size graft site may have a different outcome than the other size graft site.

Other risks related to the sinus augmentation procedure, implant placement and follow up evaluations are the following:

Local anesthesia: Although adverse reactions are rare, they may include numbness for an extended amount of time, pain, discomfort and bruising. Even more rarely, infections may be caused by the administration with the local anesthetic. (Standard of Care)

Sinus augmentation procedure: The procedure itself called lateral window approach, will entail an elevation for an extended gingival flap for access, ostectomy in the lateral maxillary wall of the sinus and elevation of the Schneiderian membrane. Risks of perforation of the membrane are evaluated at 20% and depends on the extent of them, might require to abort the procedure and come back in 4 months to re-elevate requiring the patient to go through twice of the same procedure. There is also a risk of post-operative infection, some nasal bleeding or intra-operative bleeding and pain which all can be controlled. The patients will be placed on antibiotic for 14 days as a precautionary procedure starting one day before and continuing till finishing the prescribed dose. (Standard of Care)

X-rays:
All the intraoral x-rays are standard of care.

There will be 3 CBCT scans. The first scan is a pre-operative diagnostic and is standard of care. The second scan is taken right after the sinus augmentation procedure and is for research purposes. When the contralateral sinus is performed at the same visit then there will be one CBCT scan for both sinuses. In the case were the contralateral sinus will be performed at a consequent visit then another limited field of view (FOV) CBCT will be performed. The third scan is performed 8 months after the sinus augmentation surgery as per standard of care prior to implant placement for evaluation and pre-surgical planning.

There is very little risk associated with dental x-rays. The risk involved is exposure to a very low dose of radiation. Routine safety techniques will be used including the placement of a lead apron and a thyroid collar to protect a subject from radiation. Periapical radiographs of the implant site will be taken using a bite plane/paralleling device preoperatively, intraoperatively and at the follow up visits. These periapical radiographs are standard implant evaluation procedures.

A CBCT will take place at visit 1 as a standard preoperative evaluation procedure. The CT scan will be used to assess the sinus quality, amount of crestal bone and the presence of arterioles in the lateral wall of the sinus. A CBCT will be taken immediately after the procedure to assess the integrity of the graft placement and establish the height achieved. This will help us compare with the third CBCT which will be taken at 8 months mark about the volume changes and loss of height due to graft shrinkage.

The CBCT scan used for both sides maxillary scans is 80x80 mm FOV, The kVp is 90 and mA is 5. The CTDI number for this field of view and exposure is 6.61mGy. For one side maxillary scans, 60x60 mm FOV with CTDI number of 5.74mGy.

Subjects will have exposure to low radiation from the CBCT scans. The risk from this amount of radiation is less than the risk from everyday exposure to the sun. The risks of receiving very small doses of radiation are thought to be low. However, these risks are not actually known. Pregnant women will not be included in this study because this study uses ionizing radiation (x-rays) as part of the examination. It is possible that this particular procedure may involve risks to the embryo or fetus. Women of childbearing potential will be asked to verbally confirm they are not pregnant prior to all x-rays. As per the PIs discretion, women of childbearing potential will be required to perform a pregnancy test to verify the subject is not pregnant, prior to the CT scans. Subjects of childbearing potential will be required to use birth control for the duration of the study.

Bone core harvesting (Research purposes): Using a trephine bur similar in width to the 2.5mm pilot drill (as per standard of care) a bone core of at least 5 mm long is harvested from inside the grafted sinus. The risks associated with this procedure are the same with the implant placement.

Dental implant placement (Zimmer Biomet Trabecular Metal Dental Implant)**:** Potential complications that occur with surgical procedures used to place implants include: mild discomfort, soreness or pain at implant placement site, swelling of the site, wound infection (fever or chills), bleeding, loosening of the implant (implant failure), vessel injury, or nerve injury which may cause numbness. In rare cases, the numbness may be prolonged or permanent. Although most dental implants are successful (greater than 90%), a small minority fail and have to be removed in less than five years. (Standard of Care)

Use of graft material (Research purposes): The minimal risk of the use of the graft material is further supported by numerous studies that have been performed validating the effectiveness of the Tutoplast® Process in eliminating pathogens and the potential for disease transmission. Since the commercial introduction of the Tutoplast process, more than 30 years ago, more than one million RTI Biologics tissue implantations have been performed. In addition, the process has been evaluated and described in more than 450 clinical publications, involving more than 4,000 patients and long-term data spanning up to 15 years. The numerous validations performed by independent organizations confirm the quality and safety of the Tutoplast process and its efficacy in inactivating prions, viruses and other agents responsible for transmittable diseases. Contaminant cells are ruptured and washed away during the process, exposing the RNA/DNA and enveloped and non-enveloped viruses. The process also breaks down the RNA and DNA chains into fragments so short that they are not capable of replication and disease transmission. The process has been proven to be effective in eradicating more than 12 log of infectivity. Given that the highest level of contamination recorded in an end-stage AIDS patient was seven log, the Tutoplast process provides a safety margin of five log or 100,000 times greater than necessary to eliminate this highest HIV viral load. (Schoepf C. The Tutoplast® Process: A Review of Efficacy)

Medications: Antibiotic use can cause nausea, vomiting, diarrhea and very rarely, anaphylaxis. Subjects will be given instructions to immediately stop use of antibiotics, if severe gastrointestinal or allergy type symptoms develop. For the chlorhexidine mouthwash, subjects may develop dental staining or a change in taste sensation. (Standard of Care)

Probing pocket depth: The examination of the implants and gums will involve procedures that are routine in dental practice. The gum around each implant will be measured using a standardized dental instrument. The risks from this procedure may include minor discomfort or pain during and after the procedures and minor bleeding, inflammation, and swelling of the gums. (Standard of Care)

1.5.1 Potential benefits

There will be no direct benefit to the subjects from the participation in the study. The knowledge gained from this study will help to define optimal grafting protocols, and therefore be a benefit to society.

2 Study Objectives

Primary Objective
To determine the effects of small and large bone graft particles vs large particles alone on percent vital bone, percent residual graft material, and bone graft volume, measured histologically from bone biopsies of the grafted site taken at the time of dental implant placement from subjects undergoing sinus augmentation for the placement of dental implants

Secondary Objective
To observe clinical and radiographic bone gain in order to calculate bone volume differences between conditions and the implant survivability.

3 Study Design

3.1 General Design

The proposed study is a Randomized, single-masked, split-mouth, single center study.

About 20 subjects will be screened in order to randomize 10 study subjects. 10 patients who needing bilateral sinus augmentation procedure using the lateral window technique will be randomized using computer generated randomized technique.

Pre-surgical Plan:

All procedures below are standard of care. Cone beam computed tomography (CBCT) scans are obtained for each patient (NYUCD radiology department). Standardization was done for the radiographic evaluations and measurements are for each patient is made using a radiographic guide. In cases of abnormal thickening of the membrane, suspected cysts or tumors in the sinus, patients are referred to an otolaryngologist (ENT). All patients are prescribed antibiotic and Flonase to be initiated one hour prior to the surgery (Augmentin 875 mg two times a day for 10 days; or ciprofloxacin 500 mg two times a day for 10 days in case of penicillin allergy) in order to minimize risk of infection and to control postoperative discomfort.

Surgical Procedure:

The sinus augmentation procedure is standard of care.
The use of different size and type (cortical or cancellous) of bone graft material for the two sites in order to evaluate the difference in outcome (if any), is for research purposes.
On the day of the surgical procedure, patients are instructed to rinse with chlorhexidine digluconate 0.12% (Peridex) solution for 30 seconds. Betadine is applied over three quarters of their faces prior to the initiation of the surgery. The procedure is performed under local anesthetic: 2% lidocaine with 1:100,000 epinephrine. A full thickness flap is elevated over the buccal aspect, exposing the lateral wall of the maxillary sinus. An oval-shaped osteotomy is constructed on the lateral surface of the sinus wall using Piezo with sterile saline irrigation. Using specialized curettes, the Schneiderian membrane is carefully elevated and gradually detached along the inferior wall to the medial-anterior walls and extended posteriorly until sufficient space is made for future implant placement. A mixture of 25% small-particle cortical allograft, 25% large-particle cortical allograft, 25% small-particle cancellous allograft, and 25% large-particle cancellous allograft is used for one sinus (Zimmer Biomet). The contralateral sinus will have 100% large particle cancellous allograft (Zimmer Biomet). The allografts are hydrated in sterile saline solution and packed using little pressure from the anterior to the posterior part of the sinus cavity. A resorbable Pericardium membrane (Puros CopiOs pericardium, Zimmer Biomet) is extended at least 3mm beyond the limits of the lateral window. Primary closure of the flap is achieved using 4.0 vicryl sutures. Provisional fixed or removable appliances are relieved over the edentulous areas before reinsertion.

Post-operative Care and Follow-Up:

All procedures below are standard of care. All patients are provided with verbal and written post-operative instructions following the sinus augmentation procedure. Patients are instructed to continue the antibiotic regime for a total of 14 days and to take Tylenol ES or Ibuprofen 800 mg, or a combination of both staggered as needed for pain management. Patients are seen for evaluation one week after the surgery. Sutures are removed at a two-week follow-up visit. Thereafter, patients return for follow-up visits at 1, 3, and 6 months post-operatively. If the contralateral sinus augmentation procedure was not done at the same time, it will be done no later than 6 weeks following the first surgery.

Bone Core Harvesting and Implant placement:

After 8 months, a post-operative CBCT is taken as part of standard of care in order to determine the bone gain. The CBCT will be taken as one full maxillary arch in case the two sinuses were done at the same time of surgery or as a separate sectional in case they were done apart but always for each at the six month mark. Dental implant placement is completed under local anesthesia. In case of severe anxiety, implants can be placed while patients are under conscious sedation. A crestal incision is made and a full-thickness envelope flap is elevated. A surgical guide is used for both core harvesting (Research purposes) and implant placement. Using a trephine bur similar in width to the 2.5mm pilot drill, a bone core of at least 5mm long is harvested from inside the grafted sinus. Following core harvesting, the bone cavity is further prepared for a dental implant (Zimmer Biomet Trabecular Metal Dental Implant) and the implant is placed according to the manufacturer's recommendations (Standard of care).

The harvested bone core will be fixed in 10% buffered formalin for 10 to 12 hours and cut into thinly ground longitudinal sections using a precision cutting instrument (Microtome;NanjingEverich Medicare Import & Export, Co., Ltd, Nanjing, China). The specimens will be dehydrated in an ascending series of alcohol rinses and embedded in a glycolmethacrylate resin (Techonovit 7200 VLC; Kulzer, Wehrheim, Germany). After polymerization, specimens are longitudinally cut into 150-mm-thick sections with a high-precision diamond disc and then ground down to about 30 mm in thickness with a specially designed grinding machine. The resulting slides are stained with hematoxylin and eosin and sent to the pathology department at NYUCD for histologic analysis. Quantitative histomorphometry is accomplished using software (OsteoMeasure; OsteoMetrics, Inc.,Atlanta,GA),which interfaced with a light fluorescence microscope (eg, Olympus TIRFM; Olympus Corporation, Tokyo, Japan) and digital camera (eg, Olympus Microfire; Olympus Corporation). Quantitative histology of hematoxylin and eosin-stained slide sections are assessed according to the methods of Parfitt et al for various histology features and scored using a stratified 5-point scale and a simplified 2-point scale that collapsed findings into 2 broad categories for clinical relevance

3.2 Primary Study Endpoints

The quality of bone that is generated: bone vitality, % of residual bone graft material, % of inflammatory tissue, if any.

3.3 Secondary Study Endpoints

We will be checking for bone volume stability through CBCT analysis comparing it from the time of placement, 8 months post-grafting and one-year post implant insertion.

3.4 Primary Safety Endpoints

Not applicable. These products are already commercially available and FDA approved.

4 ADMISSION CRITERIA

4.1 Inclusion Criteria

1. Age - 25 to 65 years.

2. Good physical health

3. Capable of maintaining good oral hygiene

4. Missing posterior maxillary teeth on both sides and less than 5mm of residual jaw bone requiring maxillary sinus augmentation prior to dental implant placement

5. Capable and willing to give informed consent

4.2 Exclusion Criteria

1. The presence of underlying medical conditions that may pose an undue risk for sinus surgery.
2. Patients with untreated oral infections.
3. Pregnant and lactating females.
4. Individuals who have the habit of smoking and/or tobacco chewing.
5. Patients not willing to participate in the study.

4.3 Subject Recruitment

Potential subjects are regular patients at NYUCD Department of Periodontics and Implant Dentistry and completing planned treatment. Subjects will be offered the opportunity to participate in a randomized, split mouth study comparing bone graft particle size. Written and verbal consent will be obtained. Patients/subjects will be free to 'opt out' of the study without consequence to their clinical care.

Both sizes of graft material that will be used for the study are also utilized by the clinicians for sinus augmentation procedures. To date there are no specific guidelines as to which particle size is more favorable and therefore should be exclusively used for the sinus augmentation procedures.

Bone core will be collected for research purposes during your implant surgery. These bone specimens are otherwise discarded. Personal identifying information will not be used in the analysis. Bone specimens will be coded and not identifiable by laboratory personnel or clinical investigators in this study. Only authorized study personnel will have access to the specimen-coding scheme, which will be kept in a locked file cabinet accessible only to the study investigators. No patient likenesses or personal identifying information will be used in publications or presentations.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects will be monitored for satisfactory healing of the treated sites. If a subject has an adverse event resulting in bone graft failure, appropriate steps will be taken to resolve the clinical complication. Should a test bone graft sites be deemed a failure, the subject will be offered to repeat the procedure after an appropriate healing interval. In such cases, the subject will remain enrolled in the study until completion. If a subject elect to refuse further study participation, the subject will be terminated from the study and offered alternative standard treatment options. Upon withdrawal from the study, an additional participant will be recruited in order to maintain the necessary sample size.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who fail to return for follow up appointments will be contacted by telephone up to three times. If telephone contact fails certified letter will be sent to the subjects last known mailing address. Every effort will be made to follow up with subjects until the subject is deemed lost to follow up.

5 Study device

5.1 Description

Bone graft material will consist of four to six grams of commercially available human donor bone allograft (Puros Allograft Bone Particles, Zimmer Biomet, Palm Beach Gardens, FL USA) consisting of cortical and cancellous bone chips of both 250-1000 microns, and 1000-2000 microns size, or 1000-2000 microns size alone. The method and composition of these products has been described, both products are FDA approved and commercially available. The harvesting and processing of the graft materials is briefly described as follows:

Puros Allograft Bone Particles are sterile, dehydrated cortical and/or bone from donated human tissue. The donated human tissue utilized for this implant was recovered from a donor screened for risk factors associated with infectious diseases and medical conditions that rule out donation. The donor's blood was tested for relevant communicable diseases in a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) or equivalent and registered with the U.S. Food and Drug Admiration (FDA) for donor testing. The following test criteria were met for this donor:

REQUIRED INFECTIOUS DISEASE TESTING BLOOD TEST ACCEPTABLE RESULT
- HIV-1 / HIV-2 Antibody Negative/ Non-Reactive
- Hepatitis C Virus Antibody Negative/ Non-Reactive
- Hepatitis B Surface Antigen Negative/ Non-Reactive
- Hepatitis B Core Antibody (Total) Negative/ Non-Reactive
- Syphilis Negative/ Non-Reactive
- Human T-Cell Lymphotropic Virus I/II Antibody Negative/ Non-Reactive
- HIV-1 NAT-TMA Negative/ Non-Reactive
- HCV NAT-TMA Negative/ Non-Reactive

A licensed physician for RTI Biologics Inc. determined that the donor met eligibility requirements. The physician utilized available relevant information which may have included, but was not limited to: family/next-of-kin interview, medical/hospital records, do- nor physical assessment, infectious disease test results, radiology/pathology reports, death certificate and autopsy report (if performed). Puros Allograft Bone Particles and the CopiOs Pericardium membrane are preserved by the Tutoplast® process which maintains the collagen matrix of native bone and undergoes 5 stages of: i. Delipidization, ii. Osmotic treatment, iii. Oxidative treatment, iv. Solvent dehydration, and v. Low dose gamma radiation is applied terminally to the product to achieve a sterility assurance level (SAL) of 10^{-6}.

5.2 Treatment Planning
4 to 6 grams of study material will be placed at the time of each sinus augmentation surgery as described in the clinical protocol. Subjects will be followed for a period of 6 months prior to harvesting of the bone graft cores prior to implant placement.

5.3 Preparation and Administration of Study Device
The bone graft particles will be prepared and mixed according to the surgical protocols set for the study. Sterile material is rehydrated with sterile saline mix, and packed into sterile bone syringes. These are used to condense the material into the sinus augmentation site at the appropriate stage of surgery.

5.4 Subject Compliance Monitoring
Subjects will be followed at routine clinical follow up visits as shown in the study steps, and monitored for adverse events. The most sensitive time is the first month after implantation which is a risk of infection. Once the first month is crossed we don't anticipate any risk but we will keep monitoring with post-operative visits and instructions on oral hygiene.

5.5 Prior and Concomitant Therapy
Subjects will have no restrictions on their current medications. There are no study medications as such, however, peri-operative antibiotics, and analgesics will be prescribed per standard of care. Prescription antimicrobial mouth rinse will be prescribed (chlorhexidine gluconate), per standard of care.

5.6 Study Materials/ Components

5.7.1: Study Material
1. Single use grafting material only.
2. The box is non-sterile and is used to protect the graft material during shipping and storage.
3. Additional product will be available in case of unexpected need during the procedure.
4. The box contains double-barrier packaged product, the package insert, patient implant stickers and Tissue Utilization Record from the box.

5. Prior to use the product will be inspected, including all packaging and labeling materials carefully including: no past expiration date specified on the product label, damaging to packaging, and/or a discrepancy in label information will be returned with flaws in the sterile barrier to RTI Biologics, Inc.
6. To prevent contamination of the implant, sterile technique for preparation and implantation will be used.

5.7.2: Storage Conditions.
The study material will be stored in a clean, dry environment at the temperature range specified on the product label and kept away from sunlight.

5.7 Randomization

This is a single (subject) masked study. Subjects will be unaware of which side of their jaw received which type of bone grafts. Laboratory technicians will be masked when analyzing the bone core samples.

Each tooth sites will be randomized 1:1 into one of the following bone grafts:

• Bone graft A: A mixture of 25% small-particle cortical allograft, 25% large-particle cortical allograft, 25% small-particle cancellous allograft, and 25% large-particle cancellous allograft is used for one sinus (N=10).
• Bone graft B: 100% large particle cancellous allograft for the contralateral sinus (N=10).

A randomization schedule established by an independent statistician affiliated with the New York University College of Dentistry.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Device tracking

Upon receipt of the study treatment supplies, an inventory must be performed and a device receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study device in a given shipment (active device or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.8.2 Storage

The study bone graft material is an approved material of the formulary at the NYU College of Dentistry, and is kept on hand in the clinic dispensary. It is available on demand. Supplies are ordered periodically by authorized staff to ensure availability during the study period.

5.8.3 Dispensing of Study-device

Study bone graft material will be prepared, and implanted into subjects during the sinus augmentation procedure according to randomization protocol. The amount of graft material used usually varies between 4 to 6 grams, depending on the clinical situation, and will be noted in the subject's dental chart and study case report form.

5.8.4 Return or Destruction of Study-Device

At the completion of the study, there will be a final reconciliation of device shipped, device consumed, and device remaining. This reconciliation will be logged on the device log form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study device. Device destroyed on site will be documented in the study files.

Since the study bone graft material is used routinely in the clinic, residual material is discarded. As such there will be no residual study material to reconcile.

6 Study Procedures

See an example of such a schedule of events at the end of this document. All procedures are standard of care unless indicated otherwise. All procedures will be performed by the study investigators who are licensed and privileged to do so.

6.1 Screening Visit (Day 0)

Subjects are patients assigned to graduate students within the Program for Advanced Education in Periodontics, an approved program of graduate study within the College of Dentistry. Subjects requiring sinus augmentation and implant placement and who agree to a treatment plan consisting of sinus augmentation and implant placement will be considered for enrollment. Subjects will be screened for eligibility during their clinical care appointment, and if deemed eligible, will be asked by their Graduate student if they are willing to participate in the clinical study. Subjects that meet inclusion and exclusion criteria and sign an approved study informed consent form will be scheduled for sinus augmentation surgery.

Cone beam computed tomography (CBCT) scans are obtained for each patient (NYUCD radiology department). Standardization for the radiographic evaluations and measurements for each patient is made using a radiographic guide. In cases of abnormal thickening of the membrane, suspected cysts or tumors in the sinus, patients are referred to an otolaryngologist (ENT) for consultation and or treatment prior to consideration for sinus augmentation. All patients are prescribed antibiotic and Flonase to be initiated one hour prior to the surgery (Augmentin 875 mg three times a day for 7 days; or ciprofloxacin 500 mg two times a day for 7 days in case of penicillin allergy) in order to minimize risk of infection and to control postoperative discomfort as per standard of care.

- Obtain informed consent of potential participant verified by signature on written informed consent form (Research purposes)
- Obtain demographic information, alcohol and tobacco use history
- Screen potential subjects by inclusion and exclusion criteria (Research purposes)
- Obtain and review medical/dental history, and concomitant medications
- Record blood pressure and pulse
- Standardized peri-apical radiographs, if needed
- Oral examination
- Alginate impressions taken for study model, wax-up, and radiographic/surgical template fabrication if not done prior to the screening visit
- Cone beam computed tomography with radiographic template (if not performed within 12 months prior to screening visit)
- Radiographic/surgical stent fabrication if not done prior to the screening visit
- Provide participants with prescriptions and specific instructions needed to prepare for first study visit

6.2 Visit 1 (Day 1) Randomization - Sinus Augmentation Surgery

All patients are prescribed antibiotic and Flonase to be initiated one hour prior to the surgery (Augmentin 875 mg three times a day for 7 days; or ciprofloxacin 500 mg two times a day for 7 days in case of penicillin allergy) in order to minimize risk of infection and to control postoperative discomfort as per standard care.

The randomization table will be used to assign the two treatment groups to either the right or left side of the mouth.

On the day of the surgical procedure, patients are instructed to rinse with chlorhexidine digluconate 0.12% (Peridex) solution for 30 seconds. Betadine is applied over three quarters of their faces prior to the initiation of the surgery. The procedure is performed under local anesthetic: 2% lidocaine with 1:100,000 epinephrine. A full thickness flap is elevated over the buccal aspect, exposing the lateral wall of the maxillary sinus. An oval-shaped osteotomy is constructed on the lateral surface of the sinus wall using Piezo with sterile saline irrigation. Using specialized curettes, the Schneiderian membrane is carefully elevated and

gradually detached along the inferior wall to the medial-anterior walls and extended posteriorly until sufficient space is made for future implant placement. A mixture of 25% small-particle cortical allograft, 25% large-particle cortical allograft, 25% small-particle cancellous allograft, and 25% large-particle cancellous allograft is used for one sinus (Zimmer Biomet). The contralateral sinus will have 100% large particle cancellous allograft (Zimmer Biomet). The allografts are hydrated in sterile saline solution and packed using little pressure from the anterior to the posterior part of the sinus cavity. A resorbable Pericardium membrane (Puros CopiOs pericardium, Zimmer Biomet) is extended at least 3mm beyond the limits of the lateral window. Primary closure of the flap is achieved using 4.0 vicryl sutures. Provisional fixed or removable appliances are relieved over the edentulous areas before reinsertion. Both sinus augmentation can occur on the same visit or can be done on different visits. If the contralateral sinus augmentation surgery is not done at this visit, then the surgery will take place during visit 4.

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Oral examination
- Local anesthesia administration
- Flap reflection
- Randomization (Research purposes)
- Sinus augmentation surgery (*if possible both sinus augmentation surgery will be performed on the same visit) (Research purposes)
- CBCT immediately after the surgery (Research purposes)
- Oral photographs
- Record adverse events: Subject will be contacted by phone within 24 hours from the surgery: During that conversation, they will be asked if they are experiencing any discomfort, oozing or bleeding, pain, discomfort, numbness of the lip. If anything sounded suspicious, they will be asked to come in for an evaluation.

6.3 Visit 2 (1 week ± 2 days) 1 week Follow-up assessments of study and safety

- Review medical and dental history, and concomitant medications
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Oral examination and evaluation of the surgical area
- Assessment of the healing process
- Documentation of any possible complications
- Standardized peri-apical radiographs, if needed
- Oral photographs

All patients are provided with verbal and written post-operative instructions following the sinus augmentation procedure. Patients are instructed to continue the antibiotic regime for a total of 14 days and to take Ibuprofen 800 mg as needed for pain management. Patients are seen for evaluation one week after the surgery. Sinus augmentation on the contralateral side is done no later than 6 weeks following the first surgery.

6.4 Visit 3 (2 week ± 2 days) 2 week follow-up assessments of study and safety

Sutures are removed at a two-week follow-up visit.

- Review medical and dental history, and concomitant medications
- Oral examination
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Removal of sutures
- Standardized peri-apical radiograph, if needed
- Oral photographs

6.5 Visit 4 (4 weeks ± 7 days) Possible Sinus Augmentation of contralateral sinus (*This visit is only done if the Sinus Augmentation of contralateral sinus was NOT performed during visit 1)

At this visit, the second sinus augmentation is performed if the contralateral sinus augmentation were not performed together during visit 1. The initial randomization scheme determines which treatment will be done on this site. The surgical preparation is done as above for the initial sinus augmentation surgery.

- Review medical and dental history, and concomitant medications
- Record of blood pressure and pulse
- Oral examination
- Local anesthesia administration
- Flap reflection
- Contralateral sinus augmentation surgery - (Research purposes)
- Standardized peri-apical radiographs, if needed
- CBCT immediately after the surgery (Research purposes)
- Oral photographs
- Record adverse events (Research purposes)
- Subject will be contacted by phone and 24 hours from the surgery: During that conversation, they will be asked if they are experiencing any discomfort, oozing or bleeding, pain, discomfort, numbness of the lip. If anything sounded suspicious, they will be asked to come in for an evaluation. (*perform only if contralateral sinus augmentation is performed during this visit)

6.6 Visit 4A (5 weeks ± 2 days) 1 week after contralateral surgery Follow-up assessments of study and safety – (*This visit is only done if the Sinus Augmentation of contralateral sinus was performed during visit 4)

- Review medical and dental history, and concomitant medications
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Oral examination and evaluation of the surgical area
- Assessment of the healing process
- Documentation of any possible complications
- Standardized peri-apical radiographs, if needed
- Oral photographs

6.7 Visit 4B (6 weeks ± 2 days) 2 weeks after contralateral surgery Follow-up assessments of study and safety – (*This visit is only done if the Sinus Augmentation of contralateral sinus was performed during visit 4)

Follow up care and suture removal is performed following the sinus augmentation

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Oral examination and evaluation of the surgical area
- Assessment of the healing process
- Documentation of any possible complications
- Standardized peri-apical radiographs, if needed
- Suture removal
- Oral photographs

6.8 Visit 5 (7 month ± 2 weeks) Pre-implant placement Visit and CBCT

Prior to the implant placement, a post-operative CBCT is taken as part of standard of care in order to determine the clinical outcome of the sinus augmentation bone graft and the clinical situation.

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Oral examination and evaluation of the surgical area
- Assessment of the healing process
- Documentation of any possible complications
- Standardized peri-apical radiographs, if needed
- Oral photographs
- CBCT
- CBCT review to determine the clinical outcome and the type of implant to be ordered
- Order of implants
- Provide participants with prescriptions and specific instructions needed to prepare for implant surgery

6.9 Visit 6 (8 month ± 7 days) Implant placement and bone core collection from both sinuses

Patients are instructed to rinse with chlorhexidine digluconate 0.12% (Peridex) solution for 30 seconds. Betadine is applied over three quarters of their faces prior to the initiation of the surgery. The procedure is performed under local anesthesia: 2% lidocaine with 1:100,000 epinephrine. In case of severe anxiety, implants can be placed while patients are under conscious sedation. A crestal incision is made and a full-thickness envelope flap is elevated. A surgical guide is used for both core harvesting and implant placement. Using a trephine bur similar in width to the 2.5mm pilot drill, a bone core of at least 5mm long is harvested from inside the grafted sinus (Research purposes). Following core harvesting, the bone cavity is further prepared for a dental implant (Zimmer Biomet Trabecular Metal Dental Implant) and the implant is placed according to the manufacturer's recommendations.

The harvested bone core is fixed in 10% buffered formalin for 10 to 12 hours and cut into thinly ground longitudinal sections using a precision cutting instrument (Microtome; NanjingEverich Medicare Import & Export, Co., Ltd, Nanjing, China). The specimen is dehydrated in an ascending series of alcohol rinses and embedded in a glycolmethacrylate resin (Techonovit 7200 VLC; Kulzer, Wehrheim, Germany). After polymerization, the specimen is longitudinally cut into 150-mm-thick sections with a high-precision diamond disc and then ground down to about 30 mm in thickness with a specially designed grinding machine. The resulting slides are stained with hematoxylin and eosin and sent to the pathology department at NYUCD for histologic analysis. Quantitative histomorphometry is conducted using software (OsteoMeasure; OsteoMetrics, Inc.,Atlanta,GA),which interfaced with a light fluorescence microscope (eg, Olympus TIRFM; Olympus Corporation, Tokyo, Japan) and digital camera (e.g., Olympus Microfire; Olympus Corporation). Quantitative histology of hematoxylin and eosin-stained slide sections is assessed according to the methods of Parfitt et al. for various histology features and scored using a stratified 5-point scale and a simplified 2-point scale that collapsed findings into 2 broad categories for clinical relevance.

Primary closure of the flap is achieved using 4.0 vicryl sutures. Provisional fixed or removable appliances are relieved over the edentulous areas before reinsertion.

All subjects are provided with verbal and written post-operative instructions following the implant procedure. Subjects are instructed to continue the antibiotic regime for a total of 14 days and to take Ibuprofen 800 mg as needed for pain management.

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Oral examination
- Local anesthesia administration
- Flap reflection
- Bone core collection with trephine bur (Research purposes)
- Implant placement (Zimmer Biomet Trabecular Metal Dental Implant)

- Standardized peri-apical radiographs, if needed
- Oral photographs
- Record adverse events: Subject will be contacted by phone and 24 hours from the surgery: During that conversation, they will be asked if they are experiencing any discomfort, oozing or bleeding, pain, discomfort, numbness of the lip. If anything sounded suspicious, they will be asked to come in for an evaluation.

6.10 Visit 7 (8 month + 2 weeks ± 2 days) 2 weeks after surgery follow-up and suture removal

Sutures are removed at two-week follow-up visit. Oral hygiene instructions are given.

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Oral examination and evaluation of the surgical area
- Standardized peri-apical radiographs, if needed
- Assessment of the healing process
- Documentation of any possible complications
- Oral photographs
- Suture removal

6.11 Follow up visit 8 (18 month ± 7 days)

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Oral examination
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Standardized peri-apical radiographs, if needed
- Oral photographs

6.12 Final study visit 9 (24 month ± 7 days) End of study assessments

- Review medical and dental history, and concomitant medications
- Record blood pressure and pulse
- Oral examination
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Provide any final instructions to participant
- Standardized peri-apical radiographs, if needed
- Oral photographs

6.13 Unscheduled and/or Early Termination visits

If necessary one or more visits will be performed at any time for post-operative care.

- Review medical and dental history, and concomitant medications
- Oral examination
- Record adverse events as reported by participant or observed by investigator (Research purposes)
- Standardized peri-apical radiographs, if necessary
- Oral photographs, if necessary

7 Statistical Plan

7.1 Sample Size Determination

Two test site bone samples will be compared with regard to microscopic measures of percent vital bone and residual graft material. The average of three histological specimens for each test sites of the subject biopsy will be calculated. Mean percent vital bone and percent residual graft material and standard deviations for each condition will be calculated. Condition comparisons will be made by two sided paired t-test..Sample size assumptions: Froum (2006) showed Puros M(SD) vital% of 28.2(14.0) and residual% of 7.7(9.2). Given 10 subjects in a repeated measures design, a paired t-test has power of 80% to detect a 1 SD difference in vital%, i.e., a 50% change from the level demonstrated by Froum et al. (2006). Nevins (2016) showed MinerOss vital% of 20.9 (5.0)%, suggesting a necessary change of 25% for 80% power in a paired t-test at p= .05.The necessary change in residual% is higher, at least a 100% change from the Froum level. Thus, previous studies indicate that a 25-50% difference may be detected between conditions in vital % and a 100% difference in residual graft with a sample size of 10 subjects, 80% power, and 95% confidence.

7.2 Statistical Methods

The primary outcomes for this study are percent vital bone, and residual graft material. Patient age, sex, and health status will be described. Two test site bone biopsies will be compared with regard to microscopic measures of percent vital bone and residual graft material. The average of three histological specimens for each test sites of the subject biopsy will be calculated. Mean percent vital bone and percent residual graft material and standard deviations for each condition will be calculated. Previous studies indicate that the primary outcome variable is normally distributed. Tests for normalcy will be done. In the event that the distributions are skewed, and appropriate non-parametric test will be used. Otherwise, comparisons of the two conditions will be made by two sided paired t-test. A p value less than 0.05 will be considered significant. Radiographic examinations will be quantified my measuring bone height at three sites at each sinus augmentation site and then averaged for analysis.

7.3 Subject Population(s) for Analysis

All randomized subjects in the study will be included in the analysis.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious adverse event should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, section 8.1).

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the study sponsor

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:

The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Follow-up report: within 48 hours:

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB

approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but **no later than 5 working days** of the protocol deviation.

- **Withdrawal of IRB approval**
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but **no later than 5 working days** of the IRB notification of withdrawal of approval.

8.3.2 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- **Unanticipated problems including adverse events that are unexpected and related**
  - Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
  - Harmful: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:
The following events also require prompt reporting to the IRB, though **no later than 5 working days**:

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more participants were placed at increased risk of harm
  - the event has the potential to occur again
  - the deviation was necessary to protect a subject from immediate harm
- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

8.4 Unblinding Procedures

In the event of an SAE the PI will be unblinded with regard to the randomization assignment. The unblinding will be reported to the IRB within 24 hours. A written narrative of the event will be submitted to the sponsor within 48 hours of the unblinding.

8.5 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The principal investigator will be responsible for data safety monitoring of this single site study. Adverse events, serious adverse events, unanticipated problems, and subject status will be reviewed at least annually after enrollment begins. Both the investigator and sponsor reserve the right to terminate the study, if the incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, both the investigator and the sponsor will assure that adequate consideration is given to the protection of the subjects' interests. Data safety monitoring summary will be submitted to the IRB at the time of annual continuation review.

9 Data Handling and Record Keeping

9.1 Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or dental implant company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, dental records (office and clinic) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by our clinical site 5 W staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Dentistry department of Periodontics and Implant Dentistry.

9.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that

have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.5 Records Retention

It is the investigator's responsibility to retain study essential documents according to approved procedures by NYU.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study may be monitored by NYU's IRB and according to operational procedures. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by a qualified personnel from NYU College of Dentistry.
- A periodic study review will be conducted annually to ensure the study is being conducted according to the study protocol, and all study activities are in compliance with the applicable federal regulations, the GCP and the ICH guidelines, and the facilities and staff at the site continue to be acceptable for the conduct of the study.
- Copies of monitoring reports maybe provided, if applicable.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB/EC members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study will be supported with product and cash payments by Zimmer Biomet. The bone graft procedure, the implant and the research procedures will be covered by the study. However, the two standard of care CBCT scans, implant crown and abutment will not be covered as part of this study.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable University conflict of interest policies.

13 Publication Plan

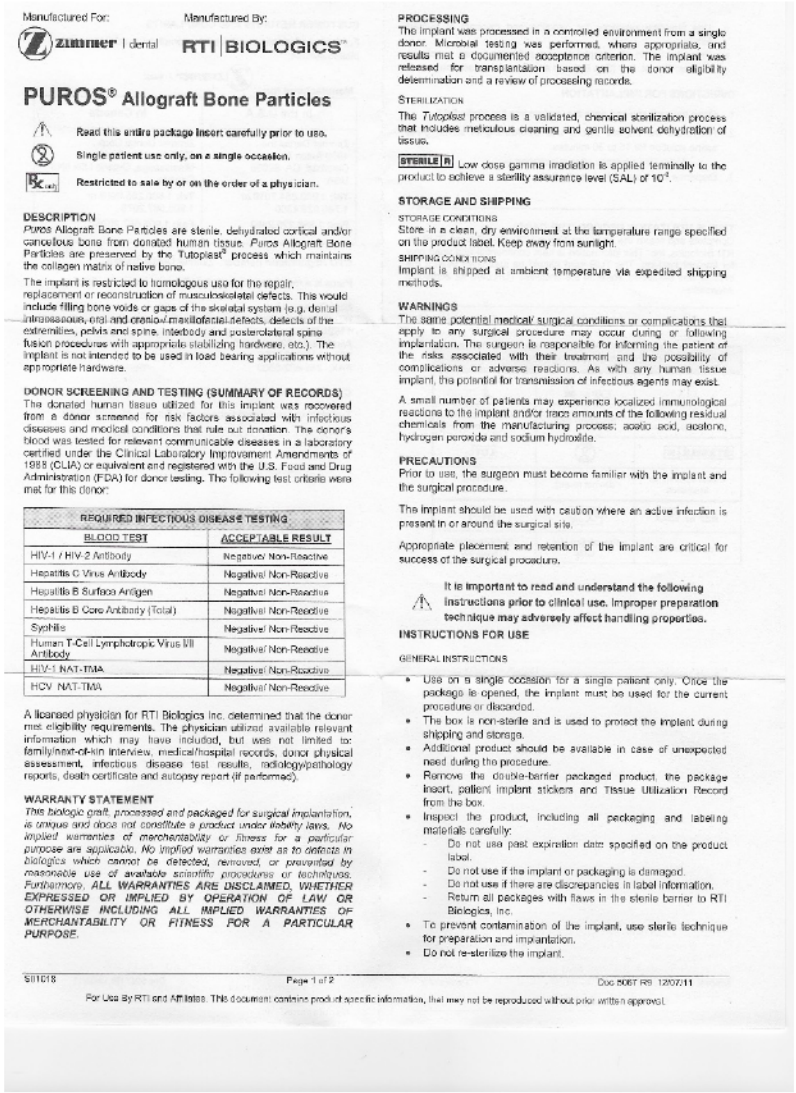
All publication plans should be discussed with Zimmer Biomet in advance.

Attachment A: Schedule of Events

	Screening Visit	Visit 1 1st sinus	Visit 2 Follow-up	Visit 3 Suture removal	Visit 4** 2n Sinus	Visit 4A Follow-up**	Visit 4B Suture removal**	Visit 5 Pre-implant	Visit 6 Implant placement & Core collection	Visit 7 Suture removal	Visit 8 Follow up	Visit 9 Final visit
Timeline	**Day 0**	**Day 1**	**1 week** ± 2 days	**2 weeks** ± 2 days	**4 weeks** ± 7 days	**5 weeks** ± 2 days	**6 weeks** ± 2 days	**7 months** ± 2 weeks	**8 month** ± 7 days	**8 month & 2 weeks** ± 2 days	**18 month** ± 7 days	**24 months** ± 7 days
Study team procedures												
Informed consent	X											
Demographics	X											
Inclusion/Exclusion Criteria	X											
Medical/Dental History	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure and pulse	X	X			X		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Standardized peri-apical radiographs	X		X	X	X	X	X	X	X	X	X	X
Oral Photographs		X	X	X	X	X	X	X	X	X	X	X
Oral Exam	X	X	X	X	X	X	X	X	X	X	X	X
Alginate impressions for study model	X											
CBCT (standard of care)	X											
Radiographic/surgical stent fabrication	X											
Prescriptions and pre-surgical instructions	X							X				
Randomization		X										
1st Sinus elevation surgery		X										
Contralateral sinus elevation surgery		X*			X							
CBCT immediately after surgery (Research)		X			X							
Suture Removal				X			X			X		
CBCT 8 months post grafting (standard of care)								X				
Implant placement and core collection from both sinuses									X			
Subject Study Close Out Visit												X

* If possible both sinus augmentation surgery should be performed on the same visit. If not possible, contralateral sinus elevation surgery will be performed during visit 4
** perform only if contralateral sinus augmentation surgery is performed during visit 4

Attachment B: PUROS package insert



Manufactured For: Zimmer | dental

Manufactured By: RTI | BIOLOGICS

PUROS® Allograft Bone Particles

Read this entire package insert carefully prior to use.

Single patient use only, on a single occasion.

Restricted to sale by or on the order of a physician.

DESCRIPTION

Puros Allograft Bone Particles are sterile, dehydrated cortical and/or cancellous bone from donated human tissue. *Puros* Allograft Bone Particles are preserved by the Tutoplast® process which maintains the collagen matrix of native bone.

The implant is restricted to homologous use for the repair, replacement or reconstruction of musculoskeletal defects. This would include filling bone voids or gaps of the skeletal system (e.g. dental intraosseous, oral and craniomaxillofacial defects, defects of the extremities, pelvis and spine, interbody and posterolateral spine fusion procedures with appropriate stabilizing hardware, etc.). The implant is not intended to be used in load bearing applications without appropriate hardware.

DONOR SCREENING AND TESTING (SUMMARY OF RECORDS)

The donated human tissue utilized for this implant was recovered from a donor screened for risk factors associated with infectious diseases and medical conditions that rule out donation. The donor's blood was tested for relevant communicable diseases in a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) or equivalent and registered with the U.S. Food and Drug Administration (FDA) for donor testing. The following test criteria were met for this donor:

REQUIRED INFECTIOUS DISEASE TESTING	
BLOOD TEST	ACCEPTABLE RESULT
HIV-1 / HIV-2 Antibody	Negative/ Non-Reactive
Hepatitis C Virus Antibody	Negative/ Non-Reactive
Hepatitis B Surface Antigen	Negative/ Non-Reactive
Hepatitis B Core Antibody (Total)	Negative/ Non-Reactive
Syphilis	Negative/ Non-Reactive
Human T-Cell Lymphotropic Virus I/II Antibody	Negative/ Non-Reactive
HIV-1 NAT-TMA	Negative/ Non-Reactive
HCV NAT-TMA	Negative/ Non-Reactive

A licensed physician for RTI Biologics Inc. determined that the donor met eligibility requirements. The physician utilized available relevant information which may have included, but was not limited to: family/next-of-kin interview, medical/hospital records, donor physical assessment, infectious disease test results, radiology/pathology reports, death certificate and autopsy report (if performed).

WARRANTY STATEMENT

*This biologic graft, processed and packaged for surgical implantation, is unique and does not constitute a product under liability laws. No implied warranties of merchantability or fitness for a particular purpose are applicable. No implied warranties exist as to defects in biologics which cannot be detected, removed, or prevented by reasonable use of available scientific procedures or techniques. Furthermore, **ALL WARRANTIES ARE DISCLAIMED, WHETHER EXPRESSED OR IMPLIED BY OPERATION OF LAW OR OTHERWISE INCLUDING ALL IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.***

PROCESSING

The implant was processed in a controlled environment from a single donor. Microbial testing was performed, where appropriate, and results met a documented acceptance criterion. The implant was released for transplantation based on the donor eligibility determination and a review of processing records.

STERILIZATION

The *Tutoplast* process is a validated, chemical sterilization process that includes meticulous cleaning and gentle solvent dehydration of tissue.

STERILE R Low dose gamma irradiation is applied terminally to the product to achieve a sterility assurance level (SAL) of 10^{-6}.

STORAGE AND SHIPPING

STORAGE CONDITIONS

Store in a clean, dry environment at the temperature range specified on the product label. Keep away from sunlight.

SHIPPING CONDITIONS

Implant is shipped at ambient temperature via expedited shipping methods.

WARNINGS

The same potential medical/ surgical conditions or complications that apply to any surgical procedure may occur during or following implantation. The surgeon is responsible for informing the patient of the risks associated with their treatment and the possibility of complications or adverse reactions. As with any human tissue implant, the potential for transmission of infectious agents may exist.

A small number of patients may experience localized immunological reactions to the implant and/or trace amounts of the following residual chemicals from the manufacturing process: acetic acid, acetone, hydrogen peroxide and sodium hydroxide.

PRECAUTIONS

Prior to use, the surgeon must become familiar with the implant and the surgical procedure.

The implant should be used with caution where an active infection is present in or around the surgical site.

Appropriate placement and retention of the implant are critical for success of the surgical procedure.

It is important to read and understand the following instructions prior to clinical use. Improper preparation technique may adversely affect handling properties.

INSTRUCTIONS FOR USE

GENERAL INSTRUCTIONS

- Use on a single occasion for a single patient only. Once the package is opened, the implant must be used for the current procedure or discarded.
- The box is non-sterile and is used to protect the implant during shipping and storage.
- Additional product should be available in case of unexpected need during the procedure.
- Remove the double-barrier packaged product, the package insert, patient implant stickers and Tissue Utilization Record from the box.
- Inspect the product, including all packaging and labeling materials carefully:
  - Do not use past expiration date specified on the product label.
  - Do not use if the implant or packaging is damaged.
  - Do not use if there are discrepancies in label information.
  - Return all packages with flaws in the sterile barrier to RTI Biologics, Inc.
- To prevent contamination of the implant, use sterile technique for preparation and implantation.
- Do not re-sterilize the implant.

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