A Prospective Study of Bone Augmentation in Extraction Sockets and Implant Surface Textures.

Study Protocol & Statistical Analysis Plan

NCT00641316

September 17, 2021

Nicolaas C. Geurs, DDS, MS, Principal Investigator

University of Alabama at Birmingham
Birmingham, Al 35294

Study Synopsis

Study Title	A Prospective Study of Bone Augmentation in Extraction Sockets and Implant Surface Textures.
Rationale	Tooth extraction is often associated with resorption of alveolar ridge height and width and with compromised soft tissue contours. An increasingly common periodontal practice combines skilled surgical technique with extraction site grafting. These procedures are thought to retard resorption of the socket volume while lending some control over bone-fill – thereby preserving the integrity of the alveolar ridge for future reconstruction with dental implants. While limited evidence-based data exist to support this premise, conflicting data suggest that the grafting materials may, in fact, impede natural post-extraction healing. In addition, the prevailing recommendation to allow grafted bone to heal for four to six months before contemplating reconstruction with dental implants is also under scrutiny and is cause for debate. Clearly, additional investigation is warranted. In an effort to establish clinical evidence this randomized-controlled clinical trial will assess and compare the efficacy of three different bone grafting applications After two months results will be compared to a control group where sites that have been allowed to heal without grafting intervention. The study will then assess the efficacy of early reconstruction with two-piece dental implants. We will evaluate the effects of two implant collar surface topographies on the longitudinal maintenance of peri-implant osseous and soft-tissue health. Follow-up evaluations will be completed at 12 and 24 months after placement of the implants.
Objectives	To evaluate hard and soft tissue healing of grafted and non-grafted extraction sockets in the aesthetic zone. To evaluate longitudinal clinical outcome of dental implants with differing collar surfaces implanted in sites 8 weeks after tooth extraction.
Hypotheses	**Hypothesis I** Bone grafted sites preserve alveolar ridge dimensions of extraction sockets more effectively than extraction sites that have healed without grafting. **Hypothesis II** The addition of growth factors to bone grafting materials will enhance osseous and soft-tissue healing. **Hypothesis III** Laser Thread Textured (LTT) dental implant will preserve longitudinal peri-implant crestal bone more effectively that implants with a Resorbable Blast Textured (RBT) surface.

Randomization	Participants will be stratified for smoking status and randomized to one of four extraction protocol groups and one of two implant groups: Extraction Groups: Group 1. Atraumatic extractions followed by saline irrigation and natural healing [Control] Group 2. Atraumatic extractions followed by Freeze-Dried Bone Allograft (FDBA) Tri-Calcium Phospate (TCP) + collaplug Group 3. Atraumatic extractions followed by FDBA/TCP/Platelet-Rich Plasma (PRP) +collaplug Group 4. Atraumatic extractions followed by FDBA/TCP/Platelet-Derived Growth Factors (PDGF) + collaplug A secondary randomization will be conducted to select one tooth site per subject to receive trephine sampling for histology evaluation. Implant Groups: Group-A. LTT collar surface topography Group-B. RBT collar surface topography
Procedures	<u>Extractions</u> Atraumatic extractions and graft/no-graft procedures will be completed following the randomization table and standardized surgical procedures. Three-dimensional images, acquired through Cone-Beam CAT-Scan (CBCT), will be captured immediately post-extraction. Prophylactic antibiotics will be dispensed, prescriptions for post-surgery antibiotics and analgesics (prn) will be written. Antibacterial mouth wash will be dispensed; written and verbal patient home-care instructions will be provided To preserve anterior aesthetics, during the healing phase, an Essix retainer will be made for each participant and inserted immediately after the extractions/grafting procedures. <u>Follow-up evaluations</u> Performed at week-1, week-2 and week-4, will include: Assessment of adverse experiences Measurement of clinical parameters Clinical photographs Suture removal at week 2 <u>Implant Placement</u> A clinical evaluation and surgical placement of implants completed at week-8 – to include: CBCT scan Prophylactic antibiotics dispensed Pre-surgical oral rinse Measurement of clinical parameters

	Clinical photographs One bone-fill specimen per patient, harvested by trephine (placed in fixative for later histological analysis) Surgeon's subjective observation of osseous fill quality (D-1-D-4) Randomized insertion of one, two-piece, dental implant per study site Immediate post-surgical intra-oral radiographs Prescriptions for post-surgery antibiotics and analgesics (prn) Antibacterial mouth wash and ice-packs dispensed Written and verbal home-care instructions <u>Post- Insertion Follow-up</u> Implant surgical follow-up assessment and suture removal will be performed after two-weeks. <u>Implants Uncovered</u> Mandibular implants will be uncovered after approximately 4 months; maxillary implants will be uncovered after approximately 6 months. <u>Implant Restoration</u> Implants will be restored in the conventional manner with aesthetically pleasing cemented single crown restorations. <u>Longitudinal Follow-up</u> Two annual follow-up evaluations will be completed at 12 months and 24 months after surgical implant placement. Each assessment will include: Standardized intra-oral periapical dental radiographs Clinical photographs Measurement of clinical parameters Assessment of soft-tissue contours Assessment of overall aesthetics Assessment of implant/restoration interface Patient satisfaction survey
Population	Eighty healthy adult patients (20 in each extraction group) of any ethnicity or gender whose treatment plan includes extraction of mandibular and/or maxillary pre-molars and/or maxillary anterior teeth and their replacement with root-form dental implants will be consecutively recruited for enrollment in the study. Only treatment of non-adjacent sites will be included in the database. Each participant may have up to four non-adjacent sites selected for inclusion as study treatment sites. Participants must be 19 years old or older with demonstrated ability to understand the proposed treatment recommendations and prognosis and be able to provide informed consent, in English, without the aid of ad hoc translation.

	Participants with a reported history of a previous malignant neoplasm, a known hypersensitivity to β-TCP or rhPDGF-BB, a Titanium metal allergy, or any other health condition or medication regimen that, in the opinion of the investigators, may adversely affect bone healing will be excluded. Women who are pregnant or nursing at the time of recruiting will be excluded.
Outcomes	Radiographic image analysis of osseous architecture changes at study sites over time Soft-Tissue aesthetic assessments Patient Satisfaction assessments Data analysis – results and conclusions Final report
Statistical Analyses	The general approach to statistical analysis of the study aims will be based on mixed-model analysis of variance (ANOVA). This approach will accommodate the inclusion of correlated observations due to study subjects potentially contributing measurements of more than one single tooth site to the analysis. The sample distributions will be examined for each outcome variable. If these distributions depart substantially from normality, transformations of the data will be evaluated. If normality cannot be established by transformation, rank-based analyses will be used. Subjects will be included as a random effect on the analyses that include multiple observations per subject. For analysis of histological data, only one tooth site per subject will be evaluated and the model will not include a random effect. Smoking status will be included in all models so that the analysis will correspond to the study's randomization strategy. For the aims in which interaction terms are of interest, significant interaction terms will be investigated using plots of least-square means and separate post-hoc analyses for individual time points.

Table of Contents

Section	Title	Page
1:	Background and Significance	6
2:	Investigational Design	9
3:	Study Population	10
4:	Study Procedures	11
5:	Tissue Biopsy & Surgical Implant Placement	15
6:	Restoration of Implants	17
7:	Longitudinal Follow-up Protocol	17
8:	Radiographic & Photographic Surveys	18
9:	Adverse Event Reporting	19
10:	Criteria for Success	19
11:	Costs to Participants	20
12:	Outcomes and Analyses	21
13:	Confidentiality	25
14:	Regulatory Issues	26
15:	Ethical Issues	27
16:	Literature Cited	28
17	Study Personnel	31
18	Signature Page	32

Appendices

A: FDA 510(k) Device Approval
B Safety and Effectiveness – GEM-21S™
C: Informed Consent
D: The Belmont Report
E: Manual of Procedures

1.0 BACKGROUND AND SIGNIFICANCE

1.1 Tooth Extraction Socket Preservation

Tooth extraction is often associated with resorption of alveolar ridge height and width and with compromised soft tissue contours[1-8]. An increasingly common periodontal practice combines skilled surgical technique with extraction site grafting. These procedures are thought to retard resorption of the socket volume while lending some control over bone-fill – thereby preserving the integrity of the alveolar ridge for future reconstruction with dental implants.

.

Limited evidence-based data exists to support a variety of bone grafting materials used to prevent the resorption of bone in the extraction socket. Autografts, allografts, xenografts and alloplasts are all considered viable options to maintain and regenerate the site[1- 6, 8].

Artzi et al.[4] evaluated the histology and histomorphometric analyses of 15 extraction sockets in 15 patients treated with cancellous porous bovine bone mineral. All procedures involved extraction sockets of anterior teeth and premolars; primary closure of the extraction sockets was achieved with a pediculated split palatal flap. The bone fill of the extraction sockets was 82.3% lamellar type bone, located in the apical portion of the sockets, and the woven type of bone found in the coronal part of the sockets. The investigators concluded that the cancellous porous bovine bone mineral was present 9 months after the procedure and that resorbability of the bone graft material needed further assessment. In a second phase of the same study, Artzi et al.[5], investigated the grafted extraction sockets by means of histochemical analysis and demonstrated the biocompatibility of the cancellous bovine bone mineral.

In another study, Froum et al.[6] grafted 30 extraction sockets and divided them into three different groups. Bioactive glass and demineralized freeze-dried bone allograft (DFDBA) were used in the two test groups;the control group received no material at all. Flaps were coronally positioned to achieve closure of the site by primary intention. The bioactive glass group exhibited 59.5% of vital bone outperforming the DFDBA and non-grafted extraction socket groups that presented 34.7% vital bone formation 6 to 8 months following the surgical procedure. The difference in vital bone was not considered statistically significant among the three groups.

Data from these studies support the potential of different bone grafting materials to preserve the alveolar ridge after extraction. Concomitant investigations, however have reported that grafting materials may, in fact, impede natural post-extraction healing[7]. Thus the most efficacious intervention remains clouded by uncertainty.

1.2 Platelet Rich Plasma

The addition of platelet rich plasma (PRP) to graft materials is gaining clinical acceptance as an added stimulus to wound healing in both osseous and soft tissues. PRP, an autologous concentration of human platelets in a small volume of plasma, consists of growth factors derived from platelets degranulation and cell adhesion proteins such as fibronectin, vitronectin and fibrin. The mechanism of action is based on the activation of transmembrane receptors of adult mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cell lines by the growth factors.

The results from twenty patients who underwent tooth extractions because of root fracture of periodontitis are reported by Anitua et al.[9] One group received PRP; in five of the ten patients in this group PRP was mixed with autologous bone to prevent tissue collapse. The remaining ten patients were left untreated and served as controls. The epithelialization in all of the cases treated with PRP was complete and significantly better than in areas treated without PRP. Osseous regeneration of mature bone was greater in quantity and quality in the PRP sites. Some limitations of this study include the absence of statistical analysis and the utilization of bone grafts in five out of ten experimental PRP sites that might have contributed to the favorable results as well as the subjective evaluation of soft-tissue healing. More recent evidence to support supplementing bone grafts with PRP was published by Marx in 2004 [10].

Despite its clinical acceptance, the scientific evidence for the use of PRP is based on promising case series and case reports. There is little data available to indicate an evidence-based advantage of grafting plus PRP compared to grafting alone.

1.3 Recombinant Human Platelet Derived Growth Factors

Recently, a combination of purified recombinant human platelet derived growth factors (rhPDGF-BB) with a beta tricalcium phosphate bone substitute [β-tcp] has been approved to aid periodontal wound healing. PDGF stimulates the mitosis of alveolar and periodontal ligament cells and β-tcp acts as the delivery vehicle that releases the growth factors over time to promote periodontal regeneration[11].

As one of 11 centers, our group[12] studied PDGF versus a β-tcp control in a prospective, randomized, double-blind, controlled human clinical trial conducted in 180 subjects. All subjects exhibited existing periodontal defects and were treated with the same surgical method. The two different experimental groups included TCP with 0.3 mg/ml of rhPDGF-BB, TCP with 1.0mg/ml; TCP carrier alone served as the control. Radiographic evaluation was performed 6 months after the surgical procedure and involved measurement of the linear bone growth in mm. The two test groups presented superior linear growth reaching to 57% and 34% bone fill compared to the control bone fill of 18%. Soft tissue healing was better in the rhPDGF-BB groups and particularly the low dose rhPDGF-BB group. We concluded that "the efficacy observed in an infected and inflamed site may indicate the potential of this regenerative modality in other bony/soft tissue wound healing applications".

1.4 Reconstruction with Dental Implants

Dental implants have been used in dentistry for decades in an attempt to reestablish function and aesthetics to areas of the mouth where natural dentition is lost [13, 14]. Materials and designs of dental implants [15, 16, 17] have evolved over the years to arrive at the optimal combination of materials, shape and surface texture that would induce permanence to the restoration.

1.5 Innovative Implant Design Features

Among the many innovations, implant surface topography has materialized as the focus of recent investigations, resulting in a body of evidence lending support to the premise that surface texturing influences osseointegration and has a positive affect on soft tissue adaptation to the implants.

Microtextured implant surfaces are thought to increase bone formation via the enhancement of osteogenesis, osteoconduction and osteoinduction processes[18]. Investigators, Buser et al[19], in a mini-pig model, demonstrated that a modified titanium implant surface resulted in similar bone-to-implant

contact to hydroxyapatite surface and Wennerberg et al [20,21,22,23], utilizing different particle size TiO2 or Al2O3, enhanced the bone formation at the implant surface in the rabbit model.

Further investigations of implant surface characteristics by Hanson and Norton[24] showed the development of pits on the implant surface. These investigators described hemispheric pits of 1 to 5μm in diameter and 1 to 5 μm in depth. The establishment of these pits is believed to increase the biomechanical interlock of implants with bone and make implant-bone interface more resistant to the forces of shear.

Other studies have shown that the modified implant surface topography alters the soft tissue- implant interface on the cellular level. The implant roughness inhibited the attachment and growth of epithelial cells while enhancing the growth of fibroblasts [25,26,27]. Implant microtextured surfaces increased bacterial colonization around implants without compromising the surrounding soft tissue health [28].

Based on this evidence, innovative microtexturing of the implant surface appears to enhance tissue integration and to promote epithelial attachment to the implant.

1.6 Resorbable Blast Texturing

The bone response to resorbable blast textured (RBT) implant surfaces have been studied in New Zealand male rabbits[29]. Twenty-four RBT implants were tested against a control group of twenty-four machined commercially pure titanium implants. All the implants were inserted into the femoral knee joint of the rabbits. The RBT implants were characterized by the plethora of osteoblastic cells residing in direct contact with the implant surface. Osteoid matrix was directly deposited on the RBT implant surface.

Another investigation by Novaes' group [30] evaluated the bone-implant interface of four different types of implant surfaces, including machined titanium, plasma spraying, hydroxyapatite coating and resorbable blast texturing. The RBT implant surfaces exhibited a statistically significant more bone-implant contact over the machined titanium implant surfaces.

1.7 Laser MicroTextured Surface

The laser thread-textured implant surface (LTT) has been recently introduced to dentistry. Little evidence-based data is currently available; one report suggests that the LTT surface developed a stronger bond and demonstrated more resistance to tensile forces [31]. Another study, utilizing a canine model, showed evidence that the laser modified surface was associated with extensive osseointegration via a high strength biomechanical interlock, less formation of fibrous tissue[32].

1.8 A Rigorous Test

Innovative implant design features coupled with novel surgical technique are challenging prevailing concepts of therapy. The dual issues: adequate, healthy, osseous tissue and the design (surface texturing) of implant devices thus remain central to the long-term success of dental implant therapy.

In an effort to establish further clinical evidence the current study will assess and compare the efficacy of three randomly assigned different bone grafting applications, including a PRP enriched material, in non-adjacent aesthetic zone extraction sockets. Sites that have healed without augmentation will serve as controls.

The study will also assess and compare the efficacy of early reconstruction with two-stage dental implant restorations and evaluate the effects of an innovative implant collar surface topography on the longitudinal maintenance of peri-implant osseous and soft-tissue.

Early reconstruction with implants placed in newly formed regenerated bone may be more prone to crestal resorption regardless of implant design. Placing implants with differing surface topographies into augmented bone may therefore, represent the most rigorous test of potential bone-preserving implant design.

2.0 INVESTIGATIONAL DESIGN

2.1 Study Design

This prospective, randomized-controlled clinical trial will test three hypotheses. One, bone grafting is an efficacious method of enhancing the development of new bone fill in extraction sockets; two, adding growth factors to grafting materials will aid osseous healing and help to preserve aesthetically pleasing soft tissue contours; and three, surface topography at the collar of implants will influence longitudinal preservation of peri-implant bone at the alveolar crest.

2.2 Objectives of the Investigation

The overall objective of this investigation is two-fold:

1. To evaluate outcomes with respect to osseous and soft tissue healing of grafted and non-grafted extraction sockets.

2. To evaluate longitudinal stability of dental implants with differing surface topographies at the collar after placement into grafted extraction sockets and sockets that have healed naturally.

2.3 Hypotheses and Specific Aims

Hypothesis I

Bone grafted sites preserve alveolar ridge dimensions of extraction sockets more effectively than extraction sites that have healed without grafting.

Specific Aims

1: Compare alveolar ridge dimensions in grafted extraction sockets to that of sites healed without grafts after 8 weeks of post-extraction healing.

Hypothesis II

The addition of growth factors to bone grafting materials will enhance osseous and soft-tissue healing.

Specific Aims

2: Assess the efficacy of bone grafting with and without enrichment with growth factors to preserve the volume of bone in extraction sockets.

3: Compare soft tissue healing between groups at week-1, week-2, week-4 and after 8 weeks of post-extraction healing

4: Assess quantitative bone fill across groups after 2 months of post-extraction healing

5: Compare qualitative bone fill across groups after 2 months of post-extraction healing.

6: Assess and compare the relationship of osseous healing and implant stability at insertion across groups after 2 months of post-extraction healing.

Hypothesis III
Laser Thread Textured (LTT) dental implant will help preserve longitudinal peri-implant crestal bone more effectively than implants with Resorbable Blast Texturing (RBT).

Specific Aims
7: Assess the efficacy of LTT and RBT surface topographies when surgically implanted into extraction sockets.

8: Assess peri-implant soft-tissue healing adjacent to LTT and RBT surfaced implants.

9: Assess changes in longitudinal crestal bone level across extraction groups and between implant groups at 12 and 24 months after surgical implant placement.

3.0 STUDY POPULATION

3.1 Entrance Criteria
Eighty healthy adult patients (20 in each group) of any ethnicity or gender whose treatment plan includes extraction of maxillary anterior teeth and/or mandibular and/or maxillary pre-molars and their replacement with root-form dental implants will be consecutively recruited for enrollment in the study.

The study will include an initial minimum of six time-sensitive, clinic visits over eight consecutive weeks. Implants will be placed 8 weeks after extractions. Following implant placement, additional visits, necessary for health maintenance and implant restoration, will be scheduled at the study dentist's discretion. Participants will return for two follow-up visits at 12 and 24 months after implant placement.

Only treatment of non-adjacent sites will be included in the database. Each participant may have up to four non-adjacent sites selected for inclusion as study treatment sites.

Participants must be at last 19 years old with demonstrated ability to understand the proposed treatment recommendations and prognosis and be able to provide informed consent, in English, without the aid of ad-hoc translation from another language. Decisionally-impaired adults and/or minors, who cannot consent for themselves, will not be enrolled; women who are pregnant or lactating at the time of enrollment will be excluded. Women will be tested for current pregnancy status.

Prior to enrollment, prospective participants must agree to be available for the entire duration of the study, be compliant with needed study-related evaluations and demonstrate a willingness to comply with strict time-line requirements. Certain health and medication exclusions apply (table 1).

Table 1 Entrance Criteria

Inclusion	Exclusion
Existence of one or more non-adjacent teeth in the aesthetic zone that are scheduled for extraction	Pregnancy or nursing at the time of enrollment
Healthy enough to undergo the proposed therapy without compromise to their existing health status	Previous malignant neoplasm
Demonstrated willingness to comply fully with protocol time-line and procedural requirements	A known hypersensitivity to β-TCP or rhPDGF-BB
At least nineteen years old	A known hypersensitivity to Titanium metal
Able to read and understand written English without the aid of ad hoc interpretation	Any health condition that in the opinion of the clinical investigators may adversely affect bone healing
Able to cognitively understand the proposed study therapy and possible prognosis	Any medication that in the opinion of the clinical investigators may adversely affect bone healing
Able to consent for their own inclusion in the study	Any indication of an inability to make autonomous decisions

3.2 Visit Sequence

The study will include a minimum of six time-sensitive clinic visits over eight consecutive weeks. Implants will be placed 8 weeks after extractions. Following implant placement, additional visits, necessary for health maintenance and implant restoration, will be scheduled at the study dentist's discretion. Participants will return for two follow-up visits at 12 and 24 months after implant placement.

4.0 STUDY PROCEDURES

4.1 Enrollment and Treatment Planning

After completing an individualized, private consent discussion and obtaining informed consent, a pre-surgical assessment will be completed. Each enrolled participant will be seen for an initial evaluation to include assessments of medical and dental conditions that will verify compliance with entrance criteria and for collection of demographic data.

Participants will be assigned a unique identification number. Information will be recorded on baseline case report forms (CRFs) developed specifically for this study.

Through consultations with prosthodontic clinicians, the documented treatment plan will be reviewed and revised if necessary to develop a therapy that will be of most benefit to the participant.

4.2 Randomization

Participants will be stratified for smoking status and randomized to one of four extraction groups; three experimental groups utilizing three different bone grafting applications and a control group where extraction sockets will be allowed to heal naturally. A secondary randomization will be conducted to select one tooth site per subject to receive trephine sampling for histology evaluation. At the time of enrollment, each participant in groups 1-4 will be further randomized into one of two implant strata.

4.3 Randomized Extraction Groups

Group 1. Atraumatic extractions followed by saline irrigation and natural healing [CONTROL]

Group 2. Atraumatic extractions followed by Freeze-Dried Bone Allograft (FDBA)/Tri-Calcium Phosphate (TCP) + collaplug

Group 3. Atraumatic extractions followed by FDBA/TCP/Platelet-Rich Plasma (PRP) +collaplug

Group 4. Atraumatic extractions followed by FDBA/TCP/Platelet-Derived Growth Factors (PDGF) + collaplug

4.4 Randomized Implant Groups

Each subject will receive two-stage dental implants with the same overall design features with two different surface treatments at the implant collar. Subjects with multiple sites will receive the same implant design in all study sites.

Group-A: Laser Thread Texturing (LTT) collar surface topography
Group-B: Resorbable Blast Texturing (RBT) collar surface topography

4.5 Pre-surgical Procedures

Oral impressions will be made and if a temporary replacement for the teeth to be extracted is required, a temporary Essix retainer will be fabricated. The Essix retainer, a removable prosthesis, will protect the healing tissue in an aesthetically pleasing manner but will not impede the clinical observation of study sites. Study casts may also be used to fabricate a surgical guide prior to implant surgery.

4.6 Surgical Extractions

All surgeries will be performed by qualified clinicians in an appropriately equipped surgical operatory located in the Periodontal Clinic at UAB School of Dentistry.

Prior to extraction surgery, participants will be given a loading dose of antibiotics based on their medical history and concomitant medications. A suggested prophylactic regimen follows:

2 gm of Amoxicillin 1 hour prior to the procedure followed by 500mg (TID) for 7 days
Patients with reported allergy to Amoxicillin:
600mg Clindamycin 1 hour prior to the procedure followed by 300mg (TID) for 7 days

The facial area will be scrubbed and the oral cavity disinfected by rinsing for 1 minute with a (0.12% chlorhexidine gluconate) antimicrobial oral rinse. Prior to extractions clinical photographs will be taken from the buccal and occlusal aspects. Photographs will be taken in a 1:1 ratio using a Nikon D-70 camera with a sunpack ringflash.

After preparation and isolation of the surgical area, anesthesia will be achieved in the region by regional block or local infiltration. Conscious sedation may be added at the surgeon's discretion to help manage patient anxiety.

The teeth will be extracted as atraumatically as possible, without raising a flap, utilizing periotomes and the Easy Extrac system. Grafting procedures will include the use of FDBA and collagen plugs in all experimental groups. In all groups, the integrity of the remaining socket walls will be assessed and measurements recorded on the surgical CRF. The sockets will be debrided and a bleeding surface created by decorticating the socket walls with either a curette or a surgical round burr.

4.7 Grafting Extraction Sockets

After extractions, sockets will be grafted according to each participant's assigned randomization group.

Group-1: Each socket will be irrigated with sterile saline and allowed to heal naturally [control group].

Group-2: Each socket will be grafted with freeze dried bone allograft (FDBA) mixed with Tri-calcium phosphate (TCP) 8:2 ratio; reconstituted with sterile saline.

4.7-2a Irrigate sockets with sterile saline

4.7-2b Pack the graft into each of the study sites using mild pressure achieving complete fill of the sockets.

4.7-2cTrim a 3mm section of collaplug and secure it over the grafted areas with 4.0 Vicryl crossing mattress sutures.

Group 3: Each socket will be grafted with an 8:2 ratio FDBA/TCP graft reconstituted with Platelet Rich Plasma (PRP).

4.7-3a Collect 9-18cc blood sample from the patient via venipuncture prepare the PRP following the Cascade Fibrinet System (Appendix A)

4.7-3b Mix PRP in the FDBA.TCP graft.

4.7-3c Irrigate sockets with sterile saline.

4.7-3d Pack the graft into each of the study sites using mild pressure achieving complete fill of the sockets

4.7-3e Trim a 3mm section of collaplug and secured it over the grafted areas with 4.0 Vicryl crossing mattress sutures.

4.7-3f Once secured in place, the soak the collaplug with PRP.

Group 4: Each socket will be grafted with an 8:2 ratio FDBA/TCP graft reconstituted with recombinant platelet derived growth factor (PDGF).

4.7-4a Irrigate sockets with sterile saline.

4.7-4b Apply PDGF into the sockets completely wetting all socket walls.

4.7-4c Mix PDGF with GEM-21S (product insert Appendix B)

4.7-4d Pack the graft into each of the study sites using mild pressure achieving complete fill of the sockets

4.7-4e Trim a 3mm section of collaplug and secure it over the grafted areas with 4.0 Vicryl crossing mattress sutures.

4.7-4f Once secured in place, soak the collaplug with PDGF.

After completion of procedures the Essix retainer (if used) will be fitted and placed.

A CBCT scan will be made to include images of each study site. Prescriptions for anti-bacterial mouth wash, antibiotics, and pain relief will be provided based on individual patient needs. An ice-pack will be dispensed. Verbal and written home care instructions will be given and the patient will be scheduled for a follow-up appointment.

4.8 Surgical Extraction Data Collection

The following data points will be collected and recorded on the surgical CRF: A description of the integrity of each of the socket walls will be recorded as follows.

4.8-1 Measurements of the Mesio-distal distance and the buco-lingual distance of the socket walls

4.8-2 Measurements of dehiscence and fenestration defects made with a UNC-15 periodontal probe in relation to the adjacent socket crest and rounded up to the nearest millimeter.

4.8-3 Wound Measurements – Mesio-distal distance and bucco-lingual distance of the soft tissue wound margins after suturing made with a UNC-15 periodontal probe and rounded to the nearest millimeter.

4.9 Post-Extraction Evaluations

Participants will return to clinic for oral evaluations as close to 7-days after the extraction/grafting procedure as possible and again at 14 days; sutures will be removed at the 14-day visit. An additional follow-up visit will be scheduled approximately 1-month following extractions. Healing will be closely monitored and appropriate data recorded on follow-up CRFs.

At each visit, medical history will be reviewed and any changes documented. Information regarding adverse events will be captured and recorded following IRB and Federal reporting guidelines. Eight weeks after the extractions, each study subject will be appointed for a second CBCT scan, a bone-fill biopsy and surgical placement of implants.

Table 2 – Study Procedures Visits -1 — 8

Procedures	**V- (-1)** Screening	**V-1** Pre-Tx	**V-2** EXT/ G	**V-3** Week 1	**V-4** Week 2	**V-5** Week 4	**V-6** Week 8 implants	**V-7** Week 10	**V-8** Expose Implant
Consent Discussion/Obtained	X								
Medical History Review		X	X	X	X	X	X	X	X
Tx Plan Review		X							
Impressions		X							
Essix Retainer		X							
Randomized to Tx Groups		X							
Biopsy site selection		X							
Pre-Surg Antibiotics			X				X		
Pre-Surg Oral Rinse			X				X		
Tooth Extraction			X						
Tx Group Procedure			X						
Venipuncture (group 3 only)			X						
Clinical Photographs			X	X	X	X	X		X
CBCT Scan			X				X		
Periapical Radiographs							X		X
Post-Surg Instructions/Prescriptions			X				X		X
Suture Removal				X				X	
AE's recorded			X	X	X	X	X	X	X
Bone Biopsy							X		
Implant Placement							X		
Implant Exposure									X

Table 3 Study Procedures Visits 9 —12

Procedures	**V-9** Impressions	**V-10** Final Restoration	**V-11** 12 month	**V-12** 24 month
Medical History Review	X	X	X	X
Impressions	X			
Clinical Photographs	X	X	X	X
Final Restoration Attached		X		
Periapical Radiographs		X	X	X
AE's recorded	X	X	X	X
Soft-tissue assessments			X	X
Pocket Depth Measurements			X	X
Patient Satisfaction			X	X

5.0 TISSUE BIOPSY AND SURGICAL PLACEMENT OF IMPLANTS

5.1 Cone Beam CT Imagery

A Cone Beam Computed Tomography (CBCT) scan will be made eight weeks after the extractions, prior to any manipulation of tissue at the study sites. The images will be used to obtain a 3-dimensional database of the participant's anatomy from the volumetric tomography. Axial, sagital, and cross-images will be reconstructed to measure tooth socket volume.

5.2 Surgical Implant Placement

The implants utilized are identical with the exception of the collar surface characteristics (Table 4). Each patient will receive either implants with an LTT or an RBT surface according the study randomization schedule.

5.3 Patient Preparation

Prior to implant surgery the subjects will be given a loading dose of antibiotics based on their medical history and concomitant medications. Local anesthesia will be achieved in the region by regional block or local infiltration. Conscious sedation may be added at the surgeon's discretion to help manage a patient's anxiety. The facial area will be scrubbed and the oral cavity disinfected by rinsing for 1 minute with a (0.12% chlorhexidine gluconate) antimicrobial oral rinse prior to the procedure.

Once the treatment areas are sufficiently anesthetized a crestal incision will be made and full-thickness flaps will be raised. With the aid of a surgical guide, the proposed implant sites will be identified; measurements of the alveolar ridge will be captured, using a UNC-15 periodontal probe and recorded on the implant surgery CRF.

5.4 Implant Selection

The diameter and length of the implant will be determined by the surgeon based on the tooth location, anatomy, and bone volume determined from the CT scan prior to placement. The collar surface will be determined by the randomization scheme.

Table 4 Implant characteristics

Implant Material:	Titanium Alloy - Ti-6Al-4V
Collar Surfaces:	Resorbable Blast Texturing (RBT) or Laser Thread Texturing (LTT)
Connection:	1.5mm deep internal hexagon
Diameters:	Ø3.5mm Ø4.0mm Ø5.0mm Ø6.0mm
Lengths:	9mm, 10.5mm, 12mm and 15mm

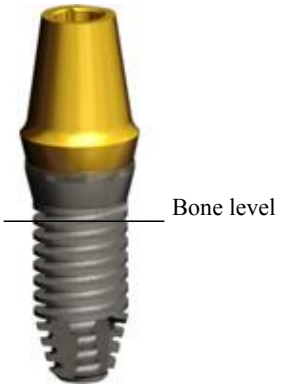
5.5 Drilling & Biopsy Technique

A standard drilling technique will be utilized except for a modification in the depth of the osteotomy and biopsy obtained from study sites described below. Copious amounts of sterile irrigant will be used in the osseous drilling procedure to prevent heating and thermal necrosis of the bone and surrounding tissue. The drill speed may be adjusted up to a maximum of 2500 rpm during the procedure. Thread forming or taping may be indicated in very dense bone and should be at a maximum of 30 rpm.

The surgeon will start with the 2mm diameter trephine drill for study sites and then proceed to increase the width with progressive depth drill depending on the implant diameter to be used at the site. The trephine with bone contained within will be harvested from the center core of one study site, per patient and will be immediately placed in fixative for later histological analysis. Vials will be labeled with the participant's ID and the date of biopsy; laboratory technicians will be blinded to knowledge of participant group assignment.

In this protocol the implant collars are to be positioned 1mm above the level of the crestal bone. This is accomplished by adjusting the depth of the osteotomy for each implant by 1mm. For example the

osteotomy depth for a 15 mm length implant should be 14mm. Since the collars of the implants are 1 mm above the bone crestal bone drills will not used in this protocol.



5.6 Implant Placement

The sterile blister pack containing the implant will drop onto a sterile field and after thorough irrigation of the site the implant will be inserted directly into the prepared bone site. After placement with the collar 1mm above the bone the insertion torque will be measured with a torque wrench and recorded on the case report forms. A cover cap will be placed on the implant and the surgical wound sutured.

5.7 ImmediatePost-Operative Procedures

Standardized intra-oral periapical dental radiographs will be made of each study site. Written and verbal post-operative instruction will be provided to each participant. An antimicrobial mouth rinse and ice packs will be dispensed. Antibiotics will be prescribed for 7 days; analgesics will be prescribed on an as needed basis at the discretion on the surgeon.

6.0 RESTORATION OF IMPLANTS

6.1 Implants Uncovered

Implants will be uncovered upon the investigator's determination that the implants are sufficiently integrated to withstand the forces of loading. In general, mandibular implants will be uncovered and restoration initiated approximately 4 months after placement; maxillary implants will be uncovered and restoration initiated approximately 6 months after placement. When the implants are uncovered, clinical photographs will be taken before, during and after the procedure; following the procedure, standardized intra-oral radiographs of each implant site will be made.

6.2 Placement of the final restoration

Each implant will be restored in the conventional manner with an aesthetically pleasing single crown restoration. Restoring materials will be selected by the restoring dentist based on discretion of the dentist and individual patient needs. Prosthetic restoration of the implants will require numerous visits to the restorative dentist over a period of one to two-months. The restoring dentist will advise when additional visits are necessary. Photographs will document each step in the restoration process and of radiographs be taken of each area when the final restoration is cemented.

7.0 LONGITUDINAL FOLLOW-UP

7.1 Post-Restoration Follow-up Evaluations (12-months and 24-months after implant placement)

Participants will return to the clinic at 12 and 24 months following implant placement. Evaluation of implant function and surrounding tissue health will be determined based on an interview with the participant, clinical examination of the study sites and an analysis of radiographic and photographic data.

At each visit, study personnel will review and update the participant's health history and record any adverse experiences; a study dentist will complete a thorough periodontal evaluation of the implant area and provide an assessment of the prosthetic attachment interface. A set of standardized periapical radiographs and clinical photographs will be made.

Case report forms will be used to record the following observations for each implant site:

- Overall soft tissue health
- Plaque and gingivitis scores (modified Löe and Sillness)
- Pocket depth and clinical attachment level
- Implant Stability
- Retention and stability of prosthetic attachment
- Overall aesthetics (soft tissue contours)
- Assessment of reported pain
- Implant survival

Each participant will complete a patient satisfaction questionnaire. Participants will be asked to report their own assessments for the following criteria:

- Comfort
- Speech
- Appearance
- Ability to taste food
- Ability to chew food
- Pain on mastication
- General satisfaction

8.0 RADIOGRAPHIC AND PHOTOGRAPHIC SURVEYS

8.1 Cone Beam Computed Tomography

Cone beam computed tomography (CBCT) images will be used to obtain a 3-dimensional database of the patient's anatomy from the volumetric tomography. Axial, sagital, and cross-images will be reconstructed to measure the tooth socket volume. Hounsfield units will be calculated to assess the relative tissue density for each study site. CBCT scans will be obtained after the completion of the extraction and grafting procedures and again at 8 weeks after the extractions.

8.2 Intra-oral radiographs

Standardized intra-oral periapical radiographs will be obtained of each site when the implants are placed and uncovered, at final implant restoration and at twelve and twenty-four months after the implants are placed. A minimum of five radiographs per study site over the duration of the study will be obtained. Additional radiographs may be obtained based on the study dentist's determination of need.

Radiographs will be used to monitor osseous health at the bone-implant interface, to verify implant position, to assess the quality of implant-attachment interface and to capture measurements of longitudinal osseous support to the implants.

8.3 Radiographic Image Acquisitions
Longitudinal measurement of osseous support to the implant sites is reliant upon serial radiographs of consistently similar quality that accurately image existing anatomy with minimal distortion over time. Ideal images for this study will center the targeted sites with at least 2mm of adjacent anatomy visible on each side of the implant.

Irregular projection geometry, variations in film positioning and mA/kVp of the X-ray beam and exposure time, coupled with poorly controlled film processing at the source (when film-based imagery is used) can influence image quality and thus can limit the accuracy of the analysis.

Taking radiographs from the same exact position at each designated interval reduces the possibility of geometric inaccuracy. Ensuring parallelism and standardization of periapical radiographs for measurement of osseous support is made possible by consistent use of a Rinn bite-block and aiming ring and careful positioning of film holding apparatus. This, coupled with fixed exposure time and standardized beam settings [milliamperage (mA) and kilovoltage (kVp)], will yield images with similar geometry and with constant density leading to a valid and dependable analysis.

8.4 Clinical Photography
Each study site will be monitored with digital photography to assess the soft tissue healing. Photographic assessment will be based on images taken at 1:1 ratio with a Nikon D-70 digital camera with a sunpack ringflash. Buccal and occlusal views will be obtained at the initial visit (prior to extraction), after completion of the grafting procedures, at 2 and 4 weeks, immediately prior to biopsy at 8-weeks, after implant insertion, at each prosthetic restorative visit, when the final restoration is attached and at four semi-annual follow-up visits.

9.0 ADVERSE EVENT REPORTING

9.1 Adverse Event Reporting
Participants will be interviewed at each visit and prompted to discuss any adverse events; such events will be recorded. In the event of a serious adverse event, the IRB will be notified per posted requirements and in full compliance with federal guidelines for research in human subjects. An event, whether study-related or not, will be assessed based on description of the event/pathology, onset, duration, severity, analgesics or other medication taken, and possible causality.

10. 0 CRITERIA FOR SUCCESS

10.1 Grafts
The success criteria for this investigation are determined as follows: Grafts will be deemed successful if there are no reported symptoms or clinical signs or of post-application allergy, toxic reactions or evidence of gross local or systemic infections.

Histological and histomorphometric analyses will provide evidence of the relative success or failure of graft materials to enhance formation of new osseous tissue in extraction sockets. Results will be compared across experimental groups and between experimental groups and controls.

A site that fails to meet the stated criteria for success, or where the width of the ridge remains too narrow for implant insertion will be re-grafted (an offer that patients may decline). The site may receive an implant at a later date but the site will be exited from the study results.

10.2 Implant Survival

At each follow-up evaluation participants will be interviewed to determine if any pain or numbness has been experienced since implant placement or has developed since the previous interview. The implant sites will be examined for any evidence of implant failure including implant suppuration and erythema.

If signs or symptoms of implant failure are observed at any time during the course of the study, a periapical radiograph will be obtained and inspected for signs of radiolucency. The investigator will make assessment of implant status and if a failure is determined, will be reported on the appropriate CRF. At the investigator's discretion a medical and/or surgical attempt to rescue the implant may be made.

10.3 Implant Success

An implant will be considered successful as long as it remains immobile when tested with instrument pressure at follow-up evaluations and offers stable anchorage to a functional prosthetic attachment. A successful implant shows no evidence of fracture or signs of peri-implant radiolucency on an intraoral radiograph (using a paralleling technique strictly perpendicular to the implant bone-interface), or persistent or irreversible signs and/or symptoms of pain, infection, neuropathies or parathesia.

11.0 COSTS TO PARTICIPANTS

11.1 Procedure Fees

No fees will be charged to participants for the, teeth extraction, socket grafting materials, implant devices, implant surgery, CBCTT scans, radiographs, photographs, bone biopsy analysis, or clinical evaluations for the entire study.

Participants will be expected to pay a **$1,000.00 restoration fee for each study site.** This one-time-only fee will cover costs related to laboratory and materials for the fabrication of the implant restoration prosthesis. This fee is to be billed to participants prior to the initiation of any surgical procedures.

Study visits are not designed to take the place of routine dental care. Over the course of the study participants will be expected to continue with regular dental check-ups with a dentist of their choice. Should the need arise patients who do not have a regular dentist of record will be referred in the appropriate manner for any non-study related dental treatment. Costs for non-study related treatment will be charged to the participant's account or to their insurance provider in the usual manner per dental school policy and will not be paid for from the study account

11.2 Payment to Participants

Participants will be paid **$50.00** after completing the 12-month visit and **$50.00** after completing the final study visit at 24 months following implant insertion.

12.0 OUTCOMES AND ANALYSES

The study is structured to provide both subjective and objective data; study sites will be followed data will be captured at placement and at 12 and 24 months after implants are placed.

12.1 Objective Data

Bone biopsies preserved in the trephines and stored in formalin will be submitted to UAB's CMBD (Name of facility) Core Laboratory. Trephine core 2x6mm will be stained with hematoxylin and eosin and processed for histologic and histomorphometric analysis. Amount of bone fill and remaining bone graft (% of new bone fill, % of residual graft and % of soft tissue) material will be determined and compared across groups.

Cone Beam Computed Technology (CBCT) will be used to capture quantitative natural bone fill and bone fill following grafting applications at each extraction site.

Image analysis software will be used to capture images from the standardized radiographs taken at 12 and 24 months following implant placement. Analysis procedures will assess the implant/bone interface and measure changes in adjacent crestal alveolar bone levels over time.

12.2 Subjective data

Observations of bone quality (D1-D-4) recorded by surgeons at implant placement.
Clinical observations of post-extraction soft-tissue healing
Clinical observations of soft-tissue and osseous response to dental implants
Clinical observations of overall aesthetic appearance

12.3 Outcome Endpoints

The primary efficacy parameter for implant success will be the duration of implant survival from surgical placement to 24 months post-placement across all groups. Measurement of bone height along the implant mesial and distal surfaces at 12 and 24 month follow-up evaluations will be captured from radiographic images and compared to same measurements at insertion. These measurements will be used to derive changes from baseline values.

Efficacy endpoints will include implant and prosthesis function as assessed by gingival health, bone levels and participant subjective satisfaction with the study therapy. Differences between groups will be calculated and used to determine if osseous changes and implant function are different across extraction groups and between implant groups.

Safety will be evaluated by clinical signs and symptoms of dental and medical events.

12.4 Statistical Analysis

The general approach to statistical analysis of the study aims will be based on mixed-model analysis of variance (ANOVA). This approach will accommodate the inclusion of correlated observations due to study subjects potentially contributing measurements of more than one single tooth site to the analysis.

The sample distributions will be examined for each outcome variable. If these distributions depart substantially from normality, transformations of the data will be evaluated. If normality cannot be established by transformation, rank-based analyses will be used.

Subjects will be included as a random effect on the analyses that include multiple observations per subject. For analysis of histological data, only one tooth site per subject will be evaluated and the model will not include a random effect.

Smoking status will be included in all models in order to account for differences in response between smokers and non-smokers, and so that the analysis will correspond to the study's randomization strategy. Comparisons between smokers and non-smokers are not a primary interest in the study.

For aims in which interaction terms are of interest, significant interaction terms will be investigated using plots of least square means and separate post-hoc analyses for individual time points.

Hypothesis 1
Differences among the four groups will be evaluated by the overall F-test for the ANOVA. Pairwise comparisons among group means will be conducted using Tukey's test. Contrasts will be constructed to address each specific aim (SA).

> SA-1: Compare alveolar ridge dimensions in grafted extraction sockets to that of sites healed without grafts after 8 weeks of post-extraction healing.

This SA will be addressed by comparing the combined mean of the three graft groups (FDBA/TCP, DDBA/TCP/PRP, FDBA/TCP/PDGF) with that of the CONTROL group by calculating a contrast and the corresponding F-test. Pairwise comparisons among means will be conducted using Tukey's test..

Hypothesis II
The addition of growth factors to bone grafting materials will enhance osseous and soft tissue healing.

> SA-2: Assess the efficacy of bone grafting with and without enrichment with growth factors to preserve the volume of bone in extraction sockets.

This SA will be addressed using mixed-model ANOVA to compare mean bone volume among the four groups. Post-hoc pairwise comparisons will use Tukey's test. The effect of growth factors enrichment will be addressed using contrasts and F-tests to compare the mean of Group-4 with those of each of the other groups. If there is not a significant difference among the group means of Groups 1-3, the combined mean of these three groups will be compared with that of Group-4.

> SA-3: Compare soft tissue healing between groups at week-1, week-2, week-4 and after 8 weeks of healing.

The analysis of SA-3 will be mixed-model ANOVA including measurements of healing made at each time points. Time will be included in the model in order to account for unequal spacing of the observational times. The statistical test that will be of primary interest will be the F-test for Group by time interaction.

SA-4: Assess quantitative bone fill across groups after 8 weeks post-extraction healing.

Qualitative bone fill will be compared among four groups using mixed-model ANOVA and the 8 week measurement only. Post-hoc pairwise comparisons will use Tukey's test.

SA-5: Compare qualitative bone fill across groups after 8 weeks post-extraction healing.

Percent new bone, percent residual graft, and percent soft-tissue will be compared among the four groups using ANOVA. For this analysis, there will be a single measurement of each of the variables per participant, so correlated observations will not be an issue in the analysis. Post-hoc pairwise comparisons will use Tukey's test.

SA-6: Assess the relationship of osseous healing and implant stability at insertion across groups after 8 weeks post-extraction healing.

This SA will be addressed by including the implant stability measure as a predictor variable in the analysis of osseous healing. The statistical test that will be of primary interest for this analysis will be the two-factor interaction of stability and group.

Hypothesis III
Laser thread-textured (LTT) dental implant will preserve longitudinal peri-implant crestal bone more effectively than implants with Resorbable blast texturing (RBT).

SA-7: Assess the efficacy of LTT and RBT surface topographies when surgically implanted into extraction sockets.

This SA will be addressed using a survival analysis approach. The primary outcome measure will be presence of signs and symptoms of infection at the implant site, since implant failure is expected to be rare to non-existent. Frequencies of occurrence of infection will be tabulated for each implant type.

Cox proportional hazards regression will be used to evaluate the rates of infection for LLT and RBT implants, allowing for adjustment for potential confounding variables and covariates. A blocking variable representing the individual subject will be included in order to reflect multiple implants per study subject.

SA-8: Assess peri-implant soft tissue healing adjacent to LTT and RBT surfaced implants

The JEMPT index will be evaluated at the time of final restoration and at 12 and 24 months follow-up evaluations. Mixed model ANOVA will be used to compare changes over time between implant types. The statistical test that will be of primary interest is the implant type by time interaction.

SA-9: Assess changes in the longitudinal crestal bone levels across extraction groups and between implant groups at 12 and 24 months after surgical placement.

The analysis for the SA will be mixed-model ANOVA, accounting for multiple observations per subject. The statistical test that will be of primary interest is the F-test for surface type by time interaction.

12.5 Power and Sample Size Considerations

Due to correlation among multiple measurements made on the same participants, the information provided by additional tooth sites within an individual is less than that provided by the initial site. For the purposes of power analysis, this may be represented by a variance inflation factor (VIF), which depends on the number of observations per cluster (individual in this case) and the intraclass correlation (ICC). The VIF is calculated as 1 + (average cluster size) X ICC. The VIF can be used to calculate an effective sample size, which is the number of independent observations that would be required to provide power equal to the larger number of correlated observations that are available to the study.

The actual sample sizes for the analysis of aims other than those based on histology data will not be known in advance, since multiple extractions pr participant will be included in the study. Histology will be conducted on a single site per participant; so variance inflation is not an issue for these measures.

Eighty participants will be recruited, each of which will contribute data on one or more extraction sites. If the average number of extractions per participant is small, say 1.5 or 2, the power of the study will not be severely reduced relative to a study with independent observations, even if the ICC is as large as 0.50. Assuming ICC = 0.50 and an average of 1.5 extractions pr participant, the total number of observations in the study would be 120, VIF=1.25, and the effective sample size would be 96, or an expected effective sample size of 24 extractions in each of the extraction groups. If there were an average of 3 extractions per participant the same assumptions would yield a total sample size of 160 VIF = 1.5, and an effective sample size of 107, or approximately 27 extractions per group.

A conservative approach to power estimation was used, assuming an effective sample size of 25 observations per extraction-implant group. Power calculations utilized the Power and Precision, release 2.00, (Borenstein, 2000) and nQuery Advisor 6.0 (Janet D. Elashoff, 1995-2005) software packages. Power to detect a “medium” effect size, corresponding to a difference between group means equal to 0.50 times the within-group standard deviation (sd) was calculated. Also, the effect size detectable with 80% power was calculated. All power estimates were based on two-sided testing at the 95% confidence level.

The power for SA-1 is largely determined by the size of control group, since the primary comparison is equivalent to a t-test of the mean of the controls vs others. Thus, the assumed effective sample sizes of 25 and 75 would yield approximatey 57% power to detect a medium effect size. The difference detectable with 80% power would be approximately 0.65sd.

Power for SA-2, SA-4 and SA-5 was based on a one-way ANOVA model. The proposed sample size would provide 52% power to detect a medium effect size or 80% power to detect an effect size equivalent to a two-group difference of 0.34sd. These approximations also apply to SA-3, with the appropriate sd being the within-group standard deviation of the changes across the observation times.

The total sample size for SA-5 would be 80, or 20 per group, since this SA is based on histology, with a single extraction per participant. Power to detect a medium effect size would be 42%. The effect size detectable with 80% power is equivalent to a two-group difference of 0.72sd.

Power for SA-6 was based on linear regression with a four-category dummy variable. If stability and group each explain 10% of the observed variance, the proposed sample size would provide 80% power to detect an increment of 8.6% in explained variance for the stability*group interaction.

Power for comparison of rates of infection signs for SA-7 was based on the chi-square test for the odds ratio. The proportions in the two groups were centered on 0.50, in order to provide a conservative estimate of power. The effective sample size of 50 per group would provide 80% power to detect an odds ratio of approximately 3.2 for the association between implant type and infection.

Power estimation for the comparison of bone height measurements (SA-7), for comparison of changes in JEMT index (SA-8) and of changes in crestal bone levels (SA-9) between the two implant types was based on a t-test. The proposed sample size would provide 70% power to detect a medium effect size, and 80% power to detect a difference of 0.565sd between the groups. For SA-8 and SA-9, sd refers to the within-group standard deviation of changes across time.

13.0 CONFIDENTIALITY

13.1 Protection of Personal Health Information

Identifiable personal health information will be protected from public dissemination and information gathered during this study will be kept confidential to the extent permitted by law. Study staff with access privileges, as well as members of the IRB may access study-related records and information that will identify participants by name.

13.2 Electronic Files

Data that link an individual to identifying information (birth date, address, telephone numbers plus pregnancy status at enrollment) will be entered into a protected electronic master file created specifically for this study. A participant log will be created and used to track each participant's progress through the study.

Each participant will be assigned a unique study-specific identification number; except for screening, names will not be written on case report forms. Screening forms that include demographic and personal information such as birthdates, address and telephone numbers will be filed in the binder with the original consent documents.

All study-related dental data will be captured on paper case report forms crafted specifically for this study. These forms will be used to record all data point measurements and assessments for the duration of the study. Data collected on the case report forms will be coded and transcribed to an electronic spreadsheet created for this study and will be used by the study statisticians for statistical analyses.

A study-specific participant file will be created to house completed paper case report forms. These forms will not be stored in the patient's dental file; however, in the interest of maintaining an accurate

of record-of-dental-treatment, treatment notes will be transcribed and inserted into each participant's dental record.

The data-collection system will be maintained by the study coordinator and will be secured through entry into a password protected computer database in the coordinator's office. Only members of the research team granted access privileges will be able to log-on to the study files.

14.0 REGULATORY ISSUES

14.1 IRB Approval

This protocol will be evaluated and approved by the responsible Institutional Review Board prior to screening/entering the first participant into the study. In accordance with federal, state, and university regulations governing research on human subjects, required documents will be submitted for IRB review by the study coordinator. Initiation of any study-related procedure (including screening) will not commence until receipt of IRB approval.

14.2 Informed Consent

The study investigators, or designee, will participant in a private English language witnessed consent discussion with all potential candidates prior to obtaining their consent to participate in this trial. Participants must demonstrate an adequate understanding of the spoken and written English language and must be able to complete the consenting process without the aid of an interpreter.

Participant's consent signature will not be obtained under the influence of strong persuasion or any effort that could be perceived as coercion; each participant will be given ample opportunity to have all their concerns addressed and all their questions answered prior to obtaining the consent signature.

Each participant must demonstrate an autonomous understanding or what it means to be a participant in a research study and must be made fully aware of the risk, benefits and costs of participation. In addition, all participants must be made aware that they can withdraw their consent at any time during the trial and for any reason without jeopardizing their future treatment at the dental school. Participants will be made aware that the consequences of early withdrawal including that the study treatment (teeth extraction, bone grafts and implant placement) are irreversible procedures.

Only the most current IRB-approved informed consent document will be used for consent signatures. The consenting process will be conducted in full compliance with University/IRB ethical policies and will follow departmental standard operating procedures. The consent form must be signed in the presence of a reliable witness, who must also sign the consent form, before any study therapy can be initiated. Each participant will be given a copy of their signed consent; the original signed consent form will remain with the investigator.

14.3 Regulatory Documents

All original study-related regulatory documents, associated correspondence and original consent documents will be housed in a study-specific regulatory binder. The binder will be secured in the coordinator's office and only study personnel will have access to the binder.

15.0 ETHICAL ISSUES

15.1 Ethical Aspects

This investigation will be conducted under good clinical practice standards and in accordance with the ethical principles and guidelines for the protection of human subjects of research as outlined in the Belmont Report and in full compliance with UAB policies and Federal Regulations and Guidelines for the conduct of research using humans.

16.0 LITERATURE CITED

1. Sclar AG. Strategies for management of single-tooth extraction sites in aesthetic implant therapy. J Oral Maxillofac Surg 2004;62:90-105.

2. Lekovic V, Kenney EB, Weinlaender M. A bone regenerative approach to alveolar ridge maintenance following tooth extraction. Report of ten cases. J Periodontol 1997;68:563-570.

3. Lekovic V, Camargo PM, Klokkevold PR, et al. Preservation of alveolar bone in extraction sockets using bioabsorbable membranes. J Periodontol 1998;69:1044-1049.

4. Artzi Z, Tal H, Dayan D. Porous bovine bone mineral in healing of human extraction sockets. Part I: Histomorphometric evaluations at 9 months. J Periodontol 2000;71:1015-1023.

5. Artzi Z, Tal H, Dayan D. Porous bovine bone mineral in healing of human extraction sockets: 2. Histochemical Observations at 9 Months J. Periodontol 2001;72: 152-159

6. Froum S, Cho SC, Rosenberg E Rorher M, Tarnow D. Histological Comparison of Healing Extraction Sockets Implanted With Bioactive Glass or Demineralized Freeze-Dried Bone Allograft: A Pilot Study J Periodontol 2002;73:94-102

7. Zubillaga G, Von Hagen S, Simon BI, Deasy MJ. Changes in alveolar bone height and width following post-extraction ridge augmentation using a fixed bioabsorbable membrane and demineralized freeze dried bone osteoinductive graft. J Periodontol 2003;74:965-975.

8. Iasella J M, Greenwell H, Miller RL, et al. Ridge preservationwith freeze-dried bone allograft and a collagen membrane compared to extraction alone for implant site development: A clinical and histologic study in humans.J Periodontol 2003;74:990-999.

9. Anitua E. Plasma rich in growth factors: Preliminary results of use in the preparation of future sites for implants. Int. J Oral Maxillofacial Implants 1999;14:529-535.

10. Marx,R.E.,2004.Platelet-rich plasma:evidence to support its use. J. Oral Maxillofac Surg. 2004; 62:489 –496

11. Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, McAllister BS, Murphy KS, McClain PK, Nevins ML, Paquette DW, Han TJ, Reddy MS, Lavin PT, Genco RJ, Lynch SE. Platelet-Derived Growth Factor Stimulates Bone Fill and Rate of Attachment Level Gain Results of a Large Multicenter Randomized Controlled Trial. J Periodontol 2005;76:2205-2215

12. Reddy MS, Giannobile WV, Nevins M, McGuire MK, Kao R, Lynch SE. Multicentered Radiographic Analysis of a Regenerative Medicine Approach to Periodontal Bone Destruction. Southeast Workshop on Tissue Engineering and Biomaterials 2nd Annual February 11-12, 2005

13. Adel R, Lejholm U, Rockler B & Brånemark PI. (1981) A 15 year study of osseointegrated implants in the treatment of the edentulous jaw. International J Oral Surgery 10:387-416,.

14. Adell, R., Eriksson, B., Lekholm, U., Brånemark, P.I. & Jemt,T. (1990) A long-term follow-up study of osseointegratedimplants in the treatment of totally edentulous jaws. International Journal of Oral and Maxillofacial Implants **5**: 347–359

15. Wataha JC. Materials for endosseous dental implants. J Oral Rehabil 1996;23:79–90

16. Lacefield WR. Current status of ceramic coatings for dental implants. Implant Dent 1998;7:315–322

17. Hench LL, Wilson J. Surface-active biomaterials. Science 1984;226:630–636

18. Cooper LF. Biologic determinants of bone formation for osseointegration: clues for future clinical improvements. J Prosthet Dent 1998;80:439-49.

19. Buser D, Schenk RK, Steinemann S, Fiorellini JP, Fox CH, Stich H. Influence of surface characteristics on bone integration of titanium implants. A histomorphometric study in miniature pigs. J Biomed Mater Res 1991;25:889-902.

20. Wennerberg A, Albrektsson T, Andersson B. An animal study of c.p. titanium with different surface topographies. J Mat Sci Mat Med 1995;6:302-9.

21. Wennerberg A, Albrektsson T, Lausmaa J. Torque and histomorphometric evaluation of c.p. titanium screws blasted with 25- and 75-microns-sized particles of Al2O3. J Biomed Mater Res 1996;30:251-60.

22. Wennerberg A, Albrektsson T, Albrektsson B, Krol JJ. Histomorphometric and removal torque study of screw-shaped titanium implants with three different surface topographies. Clin Oral Implant Res 1996;6:24-30.

23. Wennerberg A, Ektessabi A, Albrektsson T, Johansson C, Andersson B. A 1-year follow-up of implants of differing surface roughness placed in rabbit bone. Int J Oral Maxillofac Implants 1997;12:486-94.

24. Hansson S, Norton M. The relation between surface roughness and interfacial shear strength for bone-anchored implants. A mathematical model. J Biomech 1999;32:829-36.

25. Cochran, D., Simpson, J., Weber, H.P. & Buser, D.(1994) Attachment and growth of periodontal cellson smooth and rough titanium. The International Journal of Oral & Maxillofacial Implants 9: 289–297.

26. Meyle, J. (1999) Cell adhesion and spreading ondifferent implant surfaces. In: Lang, N., Karring, T. & Lindhe, J., eds. Proceedings of the 3rdEuropean Workshop on Periodontology, 55–72.Berlin: Quintessence.

27. Mustafa, K., Silva Lopez, B., Hultenby, K., Wennerberg,A. & Arvidson, K. (1998) Attachment and proliferation of human oral fibroblasts to titanium surfaces blasted with TiO2 particles. A scanning electron microscopic and histomorphometric analysis. Clinical Oral Implants Research 9:195–207.

28. Quirynen M, van der Mei HC, Bollen CM, Schotte A, Marechal M, Doornbusch GI, et al. An in vivo study of the influence of the surface roughness of implants on the microbiology of supra- and subgingival plaque. J Dent Res 1993;72:1304-9.

29. Piattelli M, Scarano A, Paolantonio M, Iszzi G, Petrone G & Piattelli *A* J Oral Implantol 2002;28:2-8

30. Novaes AB, Souza SLS, de Oliveria PT & Souza AMMS Int J Oral and Maxillofac Implants 2002;17:377-383

31. Carter DR, Giori NJ. Effect of mechanical stress on tissue differentiation in the bony implant bed. In Davies JE. The Bone- Biomaterial interface. Toronto, University of Toronto Press, 1991:367-379.

32. Britland S, Clark P, Connolly P, Moores G. Micro patterned substratum adhesiveness: A model for morphogenic cues controlling cell behavior. Exp Cell Res 1992; 198:124-129

17.0 STUDY PERSONNEL

Name	Title	Primary Role
Michael S. Reddy, DMD, DMSc	**Principal Investigator**	**Overall responsibility for conduct of the study**
Philip Vassilopoulos, DMD	**Sub-Investigator**	**Screening, dental surgery, overall patient care**
Nicolaas C. Geurs, DDS, MS	**Sub-Investigator**	**Screening, dental surgery, overall patient care**
Sandra Jean O'Neal, DMD, MS	**Sub-Investigator**	**Prosthodontist, patient care**
Perng-ru Liu, DMD	**Sub-Investigator**	**Prosthodontist, patient care**
Mark S. Litaker, PhD	**Sub-Investigator**	**Statistician/ Data Analysis**
Sandra J. Haigh, RDH, MS	**Coordinator**	**Regulatory Issues**
Sheila Akers	**Coordinator**	**Coordinating daily clinic activities, patient care, appointment scheduling, data collection**
Research Fellow	**Research Fellow**	**Screening, dental surgery, overall patient care**
Student Intern	**Student Intern**	**Assist with general patient care, appointment scheduling and data collection**
Dental Assistant	**Dental Assistant**	**General dental assisting activities**

18.0 PROTOCOL APPROVAL SIGNATURE PAGE

A Prospective Study of Differential Implant Surface Texturing and Socket Augmentation Techniques

Protocol Number FMD-07

Authored By:

Michael Reddy, DMD, DMSc
Printed Name

_____
Signature

_____
Date

Phillip J. Vassilopoulos, DMD
Printed Name

_____
Signature

_____
Date

Sandra J. Haigh, RDH, MS
Printed Name

_____
Signature

_____
Date

Nicolaas C. Geurs, DDS, MS
Printed Name

_____
Signature

_____
Date

Mark S. Litaker, PhD
Printed Name

_____
Signature

_____
Date

Approved By:

Michael S. Reddy, DMD, DMSc, Department Chair
Printed Name

_____ _____
Signature Date