Prospective, Comparative Assessment of Alveolar Bone Augmentation Using GUIDOR® Membrane in the Bound Edentulous Space

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CLINICAL STUDY PROTOCOL

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PROSPECTIVE, COMPARATIVE ASSESSMENT OF ALVEOLAR BONE AUGMENTATION USING GUIDOR® MEMBRANE IN THE BOUND EDENTULOUS SPACE

CLINICAL STUDY PROTOCOL

PROTOCOL SYNOPSIS

Sponsor
UNC School of Dentistry 5501G Koury Oral Health Sciences Building CB #7450 Chapel Hill, NC 27599-7450

Coordinating and Principal Investigator

Professor Jonathan Reside, University of North Carolina, USA

Study center(s) and number of subjects planned

The study will include a total of 60 subjects equally distributed at two centers:
Center 1: Professor Jonathan Reside, University of North Carolina, USA
Center 2: Professor Homa Zadeh, University of Southern California, USA

Study timetable

Estimated date of first subject enrolled	Q4 2015
Estimated date of last subject completed	Q3 2016/Q4 2016

Objectives

The primary objective of this study is to investigate volumetric osseous changes at 6 months following guided bone regeneration by calculating horizontal and vertical bone changes via cone beam computed tomography (CBCT).

Secondary objectives of the study are to evaluate soft tissue inflammation, soft tissue infection, and wound dehiscence..

Study design

The study is designed as a prospective, randomized controlled clinical trial. Patients will be assigned for guided bone regeneration of a single bound edentulous site to treatment group A (GUIDOR® membrane with freeze-dried bone allograft), group B (GUIDOR® membrane alone), or group C (Bio-Gide® membrane with freeze-dried bone allograft).

Target subject population

Patients in need of guided bone regeneration prior to dental implant therapy in a single, bound edentulous space within zone 14-24 or 34-44 will be included.

Investigational product

GUIDOR® membrane is a bioresorbable copolymer barrier membrane of polylactic acid blended with a citric acid ester. For this investigation 15 mm x 20 mm membranes will be utilized.

Comparator, dosage, and mode of administration

Bio-Gide® membrane is a porcine type I/type III non-cross-linked collagen bilayer membrane. The membranes are resorbed via collagenase over a 24 week period. The dense outer surface faces soft the overlying soft tissues, preventing epithelial or fibrous tissue ingrowth. The porous inner surface faces the bone and/or bone graft material and permits osteoblast ingrowth.

Mineralized freeze-dried cortical bone allograft (LifeNet Health) is a particulate bone graft material. It has a particle size of 250-1000 µm and is sterilized via Allowash XG® technology.

Duration of treatment

The study follow-up will be approximately 6-7 months. The treatment period includes guided bone regeneration in anticipation of future dental implant care. Follow-up visits following the guided bone regeneration will occur at 7 days, 14 days, 28 days, 6 months.

Outcome variables

Efficacy

Primary outcome variable:

- Horizontal and vertical bone changes at 6 months

Secondary outcome variables:

- Inflammation (refer to 4.2.2.1) or infection (refer to 4.2.2.2)
- Membrane exposure
- Soft tissue complications (refer to 4.2.2.3)

Patient reported outcomes

- Not applicable

Health economics

- Not applicable

Pharmacokinetics

- Not applicable

Safety

- Summarize all adverse events

Genetics

- Not applicable

Statistical methods

The primary outcome variables of dimensional horizontal and vertical bone changes will be analyzed by Wilcoxon rank sum test.

The secondary outcome variables assessing the presence or absence of inflammation, infection, and soft tissue complications (wound dehiscence, membrane exposure) will be analyzed by chi-square test.

1 INTRODUCTION

1.1 Background

Guided bone regeneration refers to the use of occlusive membranes to permit access of selective cell populations to an osseous defect (1). It is based on the principle that fibroblast migration occurs at a rate faster than cells with osteogenic potential. As such placement of occlusive membranes creates a secluded space to allow for bone regeneration without disruption by fibroblast infiltration (1, 2). The principles of guided bone regeneration have been used for localized alveolar ridge augmentation to increase bone dimensions prior to dental implant treatment.

Functional requirements of barrier membranes include biocompatibility, cell occlusiveness, space maintenance, integration with the host tissues, and good clinical handling (3). Two types of barrier membranes are commonly used in alveolar ridge augmentation: non-resorbable and resorbable barrier membranes. Non-resorbable membranes necessitate a second surgical procedure for membrane removal and are associated with increased complications and infection in cases of membrane exposure during the healing period. Resorbable barrier membranes offer the advantages of increased biocompatibility and integration. However, their resorption rate must be controlled so that they are able to maintain space for a prerequisite period of time to permit bone regeneration. Resorbable barrier membranes must also be associated with minimal inflammatory reactions that do not negatively affect the degree of bone regeneration achieved (3-5).

Bone replacement grafts are commonly used in conjunction with barrier membranes to aid in space maintenance while providing a scaffold for bone regeneration. A variety of bone graft options are available, including autogenic, allogenic, xenogenic, and alloplastic options. Mineralized allografts have the benefit of providing an osteoconductive scaffold with a potential for osteoinductive properties following demineralization of the graft particles by osteoclasts (6). Their use is commonplace in clinical practice due to their osteoconductive, scaffolding properties.

Following guided bone regeneration, mean horizontal ridge width gains of 4.2 mm may be anticipated with use of a resorbable barrier membrane (7). Implant survival rates of 97-100% have been reported using a staged guided bone regeneration technique (7, 8).

1.2 Rationale

This study is intended to provide statistically robust evidence that guided bone regeneration outcomes using a GUIDOR® membrane with allograft is similar or better to outcomes obtained using other commercially available barrier membranes with allograft. It is intended to define in objective and subjective terms the response of the bone and overlying soft tissues to localized ridge augmentation. To fulfill the goals of this project,

the clinical study will seek to enroll patients with a single bound edentulous space that requires ridge augmentation prior to dental implant treatment.

It has been shown that the undisturbed, healed socket will lead to a loss of alveolar bone with a mean width reduction of 3.8 mm and height reduction of 1.24 mm within 6 months (9). Schropp et. al (2003), found, according to subtraction radiography, that by 12 months, the alveolar bone present after tooth extraction decreased by up to 50% of its original width (10). Buser, et. al (1990), reported a mean gain of 1.5-5.5mm of new bone formation 6-10 months post-GBR (11). Based on these studies, a significant difference should be observed, especially between the bone grafting group and the control group.

The goal of guided bone augmentation is to provide an alveolar ridge of sufficient dimension to permit dental implant placement. The healing of these sites should occur with an absence of inflammation and other complications.

This prospective clinical evaluation will enroll sufficient participants to perform statistical analyses of primary objectives. Additional information regarding the presence or absence of inflammation, infection, or other wound healing complications will also be obtained through the projected enrollment.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to compare the horizontal and vertical changes in osseous dimension of a single bound edentulous zone following guided bone regeneration. Three different bone augmentation techniques will be used. Data will be obtained from DICOM images acquired by CBCT imaging. The dimensional location of the facial bone plate in the Z-axis and Y-axis will be reported in terms of a reference point (the mid-alveolar point positioned on a tangent drawn from the cementoenamel junctions of the mesial and distal adjacent teeth. The changes from baseline to six months will be compared.

Hypothesis: The treatment group with GUIDOR membrane with allograft is superior to comparative treatment groups (GUIDOR membrane alone or Bio-Gide® membrane with allograft).

2.2 Secondary objectives

Secondary objectives of the study are to evaluate and compare:

- Presence or absence of soft tissue inflammation within 3mm from the incision line
- Presence or absence of infection
- Membrane exposure
- Soft tissue complications, including wound dehiscence

3 STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

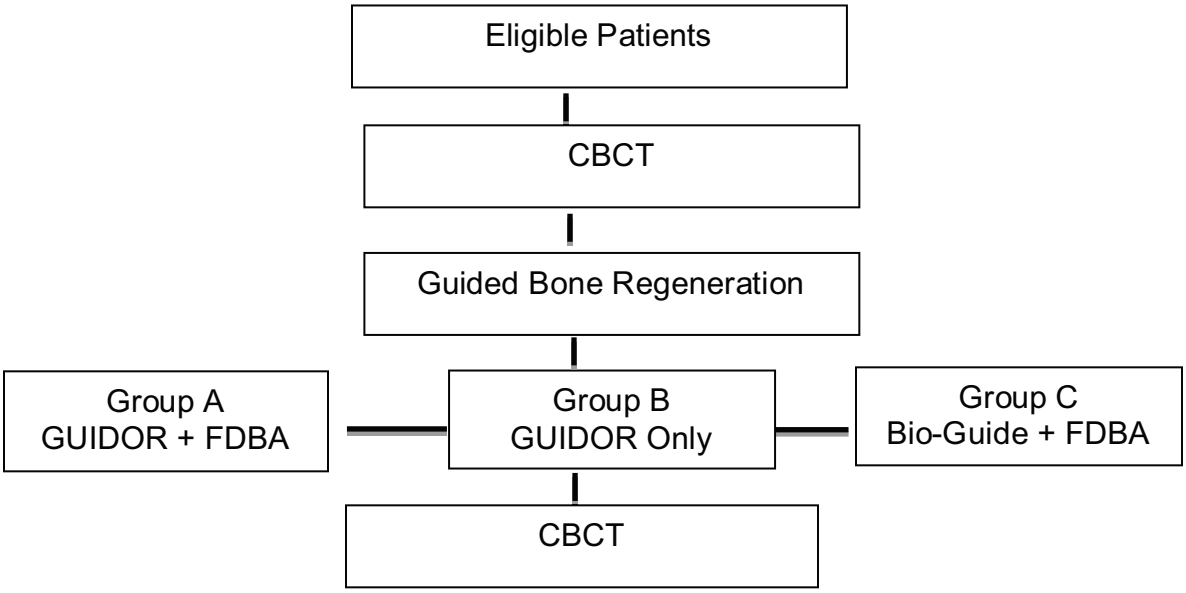
The study is designed as a randomized control prospective study with multiple study centers and is a physician initiated study.

The study population will consist of individuals requiring guided bone regeneration prior to dental implant therapy in a single, bound edentulous zone. Sites within zone 14-24 or 34-44 (maxillary and mandibular first premolars and anterior teeth) will be included.

60 subjects will be included at two centers. Each subject will be randomized into one of three groups: group A (GUIDOR® membrane and FDBA), group B (GUIDOR® membrane alone) and group C (Bio-Gide® membrane and FDBA). Each center will enroll 30 subjects, 10 per group.

The study will be a 6 month follow-up with 7 main clinic visits.

Figure 1 Study flow chart



Visit 1: Screening

Subjects in need of guided bone regeneration of a single bound edentulous site prior to dental implant surgery that are deemed eligible by meeting inclusion and exclusion criteria will be considered for treatment in this study. The single edentulous zone must lie within the region 14-24 or 34-44 (maxillary or mandibular first premolar or anterior tooth).

Before any assessment or examination is carried out for study purposes the subject must have been informed orally and in writing about the study, and have signed the appropriate consent forms. The informed consent process will be given in accordance with Declaration of Helsinki 2008 and 21 CFR Part 50. Informed consent for the research study will be given and signed on paper, as well as HIPAA authorization. All subjects for this study will be provided with a patient information sheet describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The subject will have an opportunity to ask the Investigator questions to obtain a better understanding of the study and its procedures. Then, the formal consent of the subject, using the IRB-approved consent form, will be obtained before that subject undergoes any study procedure.

Written informed consents must be obtained prior to any examination carried out for study purposes.

Individuals meeting all inclusion and none of the exclusion criteria and that have signed all appropriate consent forms will be further evaluated. Screening will entail evaluation of general dental and systemic health. It will also include a clinical and radiographic assessment of the edentulous site and the adjacent teeth. Pre-existing radiographs (e.g. panoramic and intraoral) can be used but must not be older than 6 months. Subjects with adequate alveolar ridges will immediately be scheduled for Visit 2 provided that they fulfill all inclusion and none of the exclusion criterion.

The following items will be completed during the screening visit:

- Medical, Social, and Dental History
- Oral examination
- Concomitant Medications Use: Concomitant medications which will be collected during this study consist of prescription and OTC drugs except for dietary supplements.
- Confirm radiographic assessment for inclusion and exclusion criteria

Visit 2: Cone Beam Computed Tomography Imaging (2 weeks ± 4 days from Visit 1)

Small field-of-view cone beam computed tomography (CBCT) imaging will be obtained for all patients at baseline and 6 months following the guided bone regeneration surgical procedure using the Carestream CS9300 System or equivalent system. Images will provide baseline data for horizontal and vertical bone locations. CBCT imaging will be conducted in accordance to institutional standards and technique.

Visit 3: Guided Bone Regeneration Surgery (8 weeks ± 7 days from Visit 1)

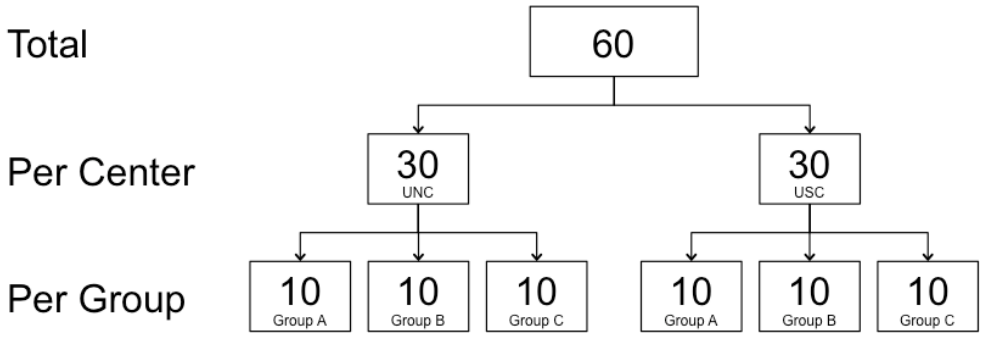
Prior to randomization, confirmation and verification of all inclusion and exclusion criteria must be completed.

The time of enrollment for this study is defined at the time the patient signs the informed consent form, meets all inclusion criteria and no exclusion criteria, is randomized and receives study treatment.

Randomization and Stratification

Subjects meeting all inclusion and none of the exclusion criteria will be randomly allocated to group A, B or C. The randomization will be per center and based on smoking status.

Figure 2 Randomization and stratification



Pre-Surgical Procedures

Buccal and crestal photographs of the planned surgical site will be obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash or equivalent device. The films must be stored in the subject's medical chart.

Pre-surgical antibiotic prophylaxis will be provided for patients at risk for infective endocarditis or with total joint replacement according to current guidelines provided by the American Dental Association, American Heart Association, and the American Academy of Orthopaedic Surgeons (9, 10).

Surgical Procedure

Sedation options will be discussed with the patient and a decision will be made to have:

- No sedation
- Oral conscious sedation

Anesthesia:

20% benzocaine topical anesthesia will be maintained for 1 minute. Infiltration anesthesia using 2% lidocaine with 1:100,000 and 2% lidocaine with 1:50,000 epinephrine will be provided. It is anticipated that 3.6 to 5.4cc will be used.

The product will be implanted according to the Instruction for Use. A crestal incision will be placed in the bound edentulous site with sulcular incisions extending to the distal line angles of the adjacent teeth. Vertical releasing incisions using a papilla sparing design will be extending to or beyond the mucogingival junction.

A full-thickness mucoperiostal flap will be elevated and extended to permit access to the edentulous site requiring bone augmentation. Periosteal release with a new #15 blade and bone decortication of the edentulous site with a 1/4 round bur will be completed.

Bone graft material and barrier membranes will be placed within the confines of the adjacent osseous architecture accordingly:

- Group A: FDBA reconstituted in saline will be used to augment the edentulous site and will be covered by a GUIDOR® membrane.
- Group B: A GUIDOR® membrane will be placed over the edentulous site.
- Group C: FDBA reconstituted in saline will be used to augment the edentulous site and will be covered by a Bio-Gide® membrane.

Following completion of bone augmentation, the flaps will be reapproximated and primary closure will be achieved using 5-0 (CV-6) ePTFE suture in the areas of the crestal and sulcular incisions and 5-0 chromic gut suture in the areas of the vertical releases. It is anticipated that horizontal mattress, vertical mattress, continuous interlocking, and/or simple loop sutures will be employed.

Post-Surgical Procedures

Post-surgery, infiltration anesthesia with 0.5% bupivacaine with 1:200,000 will be provided. It is anticipated that 1.8cc will be used.

Post-surgical antibiotic coverage will be provided to patients. It is recommended that a 7-day course of 500mg Amoxicillin every 8 hours or 300mg Clindamycin every 6 hours will be provided.

Post-surgical analgesics will be provided, it is recommended that 800mg Ibuprofen every 6-8 hours and 5/325mg Acetaminophen/Hydrocodone every 4-6 hours.

The following will be completed and documented post-surgery:

- Buccal and crestal photographs of the surgical site will be obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash or a similar product. The photographs will be stored in the subject's medical history and chart.
- Concomitant medication changes
- Adverse event assessment
- Subject instructions on post-surgical care per institutional standard of care

Visit 4: Post-Operative Visit (7 days ± 2 days post guided bone regeneration procedure)

The following will be completed and documented:

- Surgical site examination: The surgical site will be examined for inflammation within 3mm of the incision line. The site will also be assessed for membrane exposure, wound dehiscence, and infection.
- Buccal and crestal photographs of the surgical site will be obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash or a similar product. The photographs will be stored in the subject's medical history and chart.
- Concomitant medication changes
- Adverse event assessment

Visit 5: Post-Operative Visit (14 days ± 2 days post guided bone regeneration procedure)

The following will be completed and documented:

- Surgical site examination: The surgical site will be examined for inflammation within 3mm of the incision line. The site will also be assessed for membrane exposure, wound dehiscence, and infection.
- Suture material removal
- Buccal and crestal photographs of the surgical site will be obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash or a similar product. The photographs will be stored in the subject's medical history and chart.
- Concomitant medication changes
- Adverse event assessment

Visit 6: Post-Operative Visit (28 days ± 2 days post guided bone regeneration procedure)

The following will be completed and documented:

- Surgical site examination: The surgical site will be examined for inflammation within 3mm of the incision line. The site will also be assessed for membrane exposure, wound dehiscence, and infection.
- Buccal and crestal photographs of the surgical site will be obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash or a similar product. The photographs will be stored in the subject's medical history and chart.
- Concomitant medication changes
- Adverse event assessment

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Visit 7: Post-Operative Visit: Cone Beam Computed Tomography Imaging (24 weeks ± 7 days post guided bone regeneration procedure)

The following will be completed and documented during this visit:

- CBCT: Small field-of-view cone beam computed tomography (CBCT) imaging will be obtained for all patients using the Carestream CS9300 System. Images will provide post-augmentation data for horizontal and vertical bone locations.
- Surgical site examination: The surgical site will be examined for inflammation within 3mm of the incision line. The site will also be assessed for membrane exposure, wound dehiscence, and infection.
- Buccal and crestal photographs of the surgical site will be obtained using a Canon 50D digital camera body with a Canon 100mm f/2.8 macro lens and a Canon MR-14EX macro ring flash or a similar product. The photographs will be stored in the subject's medical history and chart.
- Concomitant medication changes
- Adverse event assessment

- Subject exit

Figure 3 Appointment flow chart

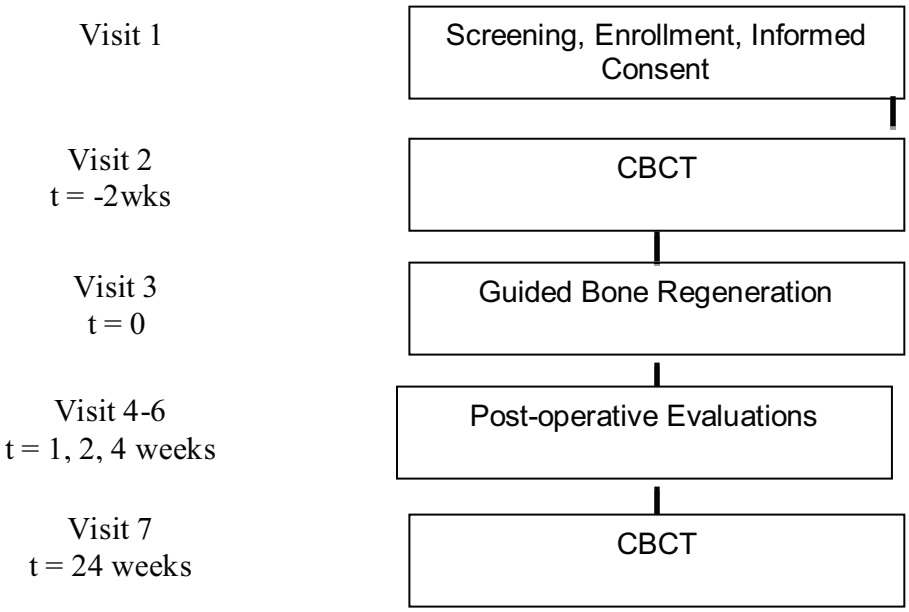

Table 1 Study plan

Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Description		Screening	CBCT	GBR	1 w post GBR	2 w post GBR	4w post GBR	CBCT- 6 m post GBR
Patient Information								
Informed consent		X						
Patient demographics		X						
Medical/surgical history		X						
Oral examination		X						
Inclusion/exclusion criteria		X						
Radiographic examination		X						
CBCT			X					X
Clinical photography				X	X	X	X	X
Randomization				X				
Guided bone regeneration				X				
Suture removal						X		
CBCT measurements	Bone dimensions		X					X
	BMD		X					X
Inflammation					X	X	X	X
Wound dehiscence, membrane exposure, and infection					X	X	X	X
Post-surgical care instructions				X				
Adverse events/Adverse device effects				X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X
Subject exit								X

3.2 Rationale and risk/benefit assessment

Possible complications following any oral surgery include thermal sensitivity, flap sloughing, some loss of crestal bone height, abscess formation, infection, pain, swelling, and complications associated with the use of anesthesia. As with any type of surgical therapy, the patient may experience discomfort for a few days.

It is necessary to further define the effects of different grafting materials on clinical outcomes following localized alveolar bone augmentation. This study will employ gold standard methods of evaluation efficacy and safety conforming to that stipulated of the medical, clinical research, and regulatory communities to demonstrate clinical benefit of GUIDOR® barrier membranes with and without bone replacement grafts. The study has been designed to treat a clinical scenario commonly encountered in clinical practice.

There are no additional risks to the patient for participating in the study which he/she would not otherwise encounter with standard guided bone regeneration procedure. The subject would be receiving tests and CBCT if he/she was not participating in this study.

Patients who receive standard guided bone regeneration whether or not participating in this study benefit from an increased alveolar ridge dimension to permit dental implant placement. The public will benefit from the study results which will help to refine the knowledge of bone healing following augmentation with different grafting material. This will help aid clinicians in the selection of materials to optimize their clinical outcomes of treatment. It will also further characterize the effects of GUIDOR® membrane on soft tissue healing while comparing its outcomes to other commonly used barrier membranes. Data acquisition includes minimally invasive collection methods, both before and after the surgical augmentation procedure.

Study selection record

Investigator(s) will keep a record of subjects who were considered for enrollment but were never enrolled (e.g., subject screening log). This information is necessary to establish that the subject population was selected without bias.

Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Provide written informed consent
2. ≥ 21 years and ≤ 75 years
3. In need of one or more implants replacing missing or non-restorable teeth in the maxilla within region 14 to 24 or the mandible within region 34 to 44
4. Edentulous for at least 6 months at study site
5. A buccal-lingual ridge width at study site of ≤ 4 mm

6. A mesial-distal distance between adjacent teeth at study site at bone level of at least 5 mm

7. A keratinized mid-buccal mucosal thickness of at least 2 mm at study site (measured buccaly at MD midline from the mucogingival junction to the projected alveoalr ridge crest)

8. Teeth adjacent (mesial and distal) to study site must consist of two stable, natural teeth without signs of periodontal bone loss (> 3 mm) and/or significant soft tissue loss

9. A minimum of twenty teeth in good repair

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Insufficient interocclusal distance for future dental implant placement and restoration

2. More than 3 mm vertical bone loss at study site as measured from the mid-buccal crest of bone on the adjacent teeth

3. Previous site development (soft and/or bone tissue) performed at the study site

4. Untreated rampant caries and uncontrolled periodontal disease

5. A history within the last 6 months of the daily use of any tobacco products besides cigarettes (smokeless chewing tobacco, e-cigarette, pipe or cigar smoking), or of smoking more than 10 cigarettes per day.

6. Current alcohol dependency, alcohol abuse or chemical dependency based on DSM-IV Criteria or drug abuse

7. Subjects having uncontrolled endocrine-induced diseases (e.g. uncontrolled diabetes mellitus and hyperparathyroidism)

8. Systemic or local disease or condition that would compromise post-operative healing and/or osseointegration

9. Use of any substance or medication that will influence bone metabolism (e.g. intravenous bisphosphonates)

10. Need for systemic corticosteroids or any other medication that would influence post-operative healing and/or osseointegration

11. History of radiation in the head and neck region > 30 Gy

12. Subject reports pregnancy or is nursing at the time of enrollment

13. Unable or unwilling to return for follow-up visits for a period of 6 months

14. Unlikely to be able to comply with study procedures according to Investigators judgement

15. Previous enrollment or randomization of treatment in the present study

16. Participation in another clinical trial within 30 days of enrollment

Restrictions

Subjects will be advised of the following restrictions during the study period:

- To avoid disruption of wound healing during the initial study period the subject should have a restricted diet for at least 14 days (printed instructions will be distributed to the subjects at Visit 3 per institutional standard of care)
- For current smokers, no more than 10 cigarettes per day are allowed

Discontinuation of subjects from treatment or assessment

3.2.1.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator
- Severe non-compliance to protocol as judged by the investigator
- Subject received further dental therapy on study site or adjacent teeth without consent of investigator (e.g. new crown, periodontal surgery, or orthodontics on adjacent teeth)
- Subject lost to follow-up

3.2.1.2 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any AEs or ADEs. If possible, they should be seen and assessed by an investigator(s). Ongoing AEs and ADEs should be followed up.

A subject will be classified as lost to follow up only if, he/she has failed to return to the required study visits and his/her dental status remains unknown, despite 3 documented attempts to contact the subject via telephone, fax, email, and certified letter.

3.2.1.3 Procedures for handling incorrect enrolled subjects

Subjects not meeting the inclusion/exclusion criteria for a study should not be enrolled into the study. If a subject is enrolled who does not meet inclusion/exclusion criteria, a protocol deviation will be completed.

3.3 Treatments

Identity of investigational product and comparators

All components are commercially available.

GUIDOR® barrier membranes are made of polylactic acid with a citric acid ester. It is double-layered; the external layer has large rectangular perforations which face the overlying soft tissues and permit connective tissue infiltration, while the inner layer has small circular perforations which face bone and inhibit fibrous tissue ingrowth. It maintains its barrier function for 6 weeks, with complete resorption occurring by 6 months. Available membrane dimensions include 15 mm x 20 mm, 20 mm x 28 mm, and 30 mm x 40 mm. The membrane is provided in a transparent plastic tray in a sealed aluminium pouch. It comes sterilized via e-beam.

Bio-Gide® barrier membranes are made from non-cross-linked type I/type III porcine collagen. It consists of a dense outer layer that inhibits fibrous tissue ingrowth and a rough, fibrous side that helps with clot stabilization and permits osteoblast cell attachment. Resorption occurs over a period of 24 weeks. Available membrane dimensions include 13 mm x 25 mm, 25 mm x 25 mm, and 40 mm x 50 mm. The membrane is provided in transparent plastic tray in a double blister pack. It comes sterilized via gamma irradiation.

Lifenet Health® mineralized cortical freeze-dried particulate bone allograft has a particle size of 250-1000 µm. Available quantities include 0.25 cc, 0.50 cc, 0.70 cc, 1.20 cc, 2.50 cc. It is sterilized via Allowash XG® technology, consisting of rigorous screening and assessment of donor tissues; cleaning with hypotonic solutions and antimicrobial reagents; decontamination, disinfection, and cleaning regimens with hydrogen peroxide and isopropanol alcohol solutions; and terminal sterilization with gamma irradiation. The particulate material comes packaged in a sterile vial in a blister pack.

GORE-TEX® sutures are expanded polytetrafluoroethylene nonabsorbable monofilament sutures. They are available in suture sizes ranging from CV-0 to CV-8. They are an inert material that elicits minimal tissue reaction.

Labeling

All grafting materials will be labeled as follows:

- “Reference number”
- “Lot number”
- “Expiration date”

The reference number and lot numbers will be recorded in clinical records (source data) and eCRF.

Storage

All study products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the study product label and product information.

3.4 Method of assigning subjects to treatment groups

Subject numbers (subject ID) will be consecutively allocated in series at day of inclusion (Visit 1). Subjects at center 1 will receive numbers starting at 101 and subjects at center 2 will receive numbers starting at 201. Enrollment will continue until 30 subjects at each center have been allocated a subject ID. If a subject discontinues, the subject number will not be reused.

Subjects will be randomized at day of alveolar bone regeneration (Visit 3). At Visit 2 all study sites in all subjects are considered equivalent. The randomization schedule will be generated using a validated computerized randomization system under the responsibility of the investigatory team. The randomization assignment will be concealed via envelope until the surgical date. Randomization will be stratified by center and smoking habit, i.e. each center will have 10 subjects in each group A, B and C, respectively with an equal number of subjects with current tobacco consumption per group. Each subject will be treated according to the treatment code in the envelope. The allocation will be revealed to the clinician only following flap elevation for the alveolar regeneration procedure.

The randomization code envelopes will be stored at each center by designated research staff.

Pre-study, concomitant and post-study treatment(s)

Systemic corticosteroids or any other medication that would compromise post-operative healing and/or bone healing are not allowed.

After surgery, mouth rinsing with 0.12% non-alcohol chlorhexidine rinse will be subscribed according to local routines.

Subjects will be given post-surgical instructions with regards to diet and oral hygiene. Oral hygiene instructions will be given to the subjects at all study visits.

Other medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator(s). The administration of all medication (excluding dietary supplements) must be recorded in the appropriate sections of the CRF.

4 MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Screening and demographic measurements

The following data will be recorded via a standard CRF:

- Date of birth
- Height and weight (Body Mass Index)
- Sex
- Race
- Relevant medical and surgical history
- Medication
- Oral examination
- Local condition of alveolus and adjacent teeth
    - Periodontal disease
    - Bone loss
    - Caries
    - Mobility
    - Crown
    - Post/core
    - Endodontic treatment
    - Existing periapical radiolucency
- Tobacco use
- Reason for tooth extraction (if known)
- Duration of edentulous period (if known)
- Previous bone graft, soft tissue graft, or apical surgery
- Opposing tooth contact in maximum intercuspation

4.2 Efficacy

Primary outcome variable

4.2.1.1 Dimensional osseous changes

The amount of horizontal and vertical bone changes will be calculated using data from DICOM images acquired by CBCT using 3D software.

4.2.1.1.1 Methods of assessment

CBCT images will be obtained at baseline (Visit 2) and 6 months following alveolar ridge augmentation (Visit 7). Using ITK-Snap 3D analysis software, the CBCT images will be aligned via superimposition of adjacent tooth structures to permit evaluation of bone changes within the bound edentulous space. One masked analyst will complete the evaluations.

4.2.1.1.2 Derivation or calculation of variable

The mid-alveolar point positioned on a tangent drawn from the mesial and distal adjacent tooth CEJs will be used as a reference point for assessment of dimensional bone changes in the Z-axis (bone width) and Y-axis (bone height). The changes in the bone dimensions between baseline (Visit 2) and 6 months (Visit 7) will be measured. The change for each study site will be compared longitudinally and the average for each treatment group will be calculated and compared among treatment groups.

Secondary outcome variables

4.2.1.2 Inflammation

The presence or absence of soft tissue inflammation in the area of ridge augmentation will be visually assessed.

4.2.1.2.1 Methods of assessment

Soft tissue erythema within 3 mm from the crestal incision in the edentulous site will be visually assessed at post-operative evaluations (Visits 4-6).

4.2.1.2.2 Derivation or calculation of variable

Erythema will be marked as either present or absent according to the clinician's judgment. The percentage of sites with or without inflammation will be calculated for each treatment group and compared longitudinally.

4.2.1.3 Infection

The presence or absence of infection in the area of ridge augmentation will be assessed through visual evaluation and palpation.

4.2.1.3.1 Methods of assessment

Infection will be assessed at post-operative evaluations (Visits 4-6). The presence of suppuration from the crestal incision or soft tissues adjacent to the localized ridge augmentation will be assessed through visual evaluation. Fluctuance in the area of the augmentation will be assessed through gentle palpation of the surgical site. (Visits 4-6).

4.2.1.3.2 Derivation or calculation of variable

Infection will be marked as either present or absent according to the clinician's judgment. The percentage of sites with or without infection will be calculated for each treatment group and compared longitudinally.

4.2.1.4 Soft tissue complications

The presence of soft tissue complications, including wound exposure or soft tissue dehiscence, will be visually assessed.

4.2.1.4.1 Methods of assessment

At each post-operative evaluation (Visits 4-6), the presence of membrane exposure or soft tissue dehiscence will be visually assessed.

4.2.1.4.2 Derivation or calculation of variable

Membrane exposure or soft tissue dehiscence will be marked as either present or absent according to the clinician's judgment.

4.3 Patient reported outcomes

Not applicable

4.4 Health economic measurements and variables

Not applicable

4.5 Pharmacokinetics

Not applicable

4.6 Safety measurements and variables

The methods for collecting safety data are described below.

Adverse Events

4.6.1.1 Definitions

The definitions of AEs, ADEs and Serious Adverse Events (SAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse Event

An AE includes any unfavorable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the clinical study. For the purposes of this study, adverse events which are considered related to the GBR procedure or related to the GUIDOR membrane will be reported. Adverse events which are not related (temporal relationship of the onset of the event, relative to the use/administration of the medical device, is not reasonable or another cause can itself explain the occurrence of the event) will not be required to be reported.

For the purposes of this protocol, the following occurrences are considered to be expected observations following guided bone regeneration procedure and will not be captured as additional complications or device related adverse events:

- Post-operative nausea determined to be procedure related or due to reactions to pain medication
- Post-operative transient headache or pain responding to standard medications
- Post-operative pain related to procedure within 7 days
- Post-operative swelling related to the procedure and determined not to be

associated with infection within 7 days of procedure.

Adverse Device Effect

An ADE is any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use of the medical device or any event that is a result of a user error. This definition also includes treatment- or procedure-related events. ADEs can only occur from the time of medical device use/administration. Here the event is related to the use of the medical device where there is a probable/definite relationship that the event may have been caused by the medical device, or treatment.

- Probably related: temporal relationship of the onset of the event, relative to the use/administration of the medical device, is reasonable and the event is more likely explained by the medical device/treatment than by any other cause.
- Definitely related: temporal relationship of the onset of the event, relative to the use/administration of the medical device, is reasonable and there is no other cause to explain the event.

Serious Adverse Event

A SAE is an AE/ADE occurring during any study phase of the medical device that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

For the purposes of this study, all Serious Adverse Events will be reported.

4.6.1.2 Recording of Adverse Events and Adverse Device Effects

At each visit, the subject will be asked an open question; "Have you had any health problems since the previous visit?"

All health problems, reported by the subject or found at the clinic visit, where the investigator believes the event to be related to the investigational medical device or treatment, must be recorded in the CRF as AEs, specifying time of onset, action taken, outcome and whether it constitutes a SAE or not.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.2, Pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that a medical device under study may have interfered with the effectiveness of a contraceptive medication.

4.6.1.3 Reporting of Serious Adverse Events

Timelines for reporting of SAEs

Investigators and other study site personnel should inform the IRB of serious adverse events per the IRB reporting requirements. It is recommended that serious adverse event be entered into the eCRF within 24 hours upon awareness of the event.

4.7 Protocol Deviations

The investigator should avoid deviating from the protocol. All deviations related to clinical investigation inclusion or exclusion criteria, conduct of the investigation, patient management, or patient assessment are to be documented on the eCRF provided for that purpose. Notification to the IRB should be documented and maintained in the clinical investigation file (as required).

4.8 Genetics

Not applicable

5 DATA MANAGEMENT

5.1 Data handling

Paper case report forms will be utilized for the study. The CRF will be completed for each included patient. The completed CRFs will not be made available in any form to third parties. The data will be reviewed by the monitor or designee and queries will be issued. The study site personnel are required to resolve any such queries.

At the end of the study, the monitor will perform final validation checks, after which Clean File will be declared.

5.2 Record retention

To enable evaluations and/or audits the investigator agrees to keep records in the Investigator's Study File (ISF), including the identification list of the participating patients, all original signed Informed Consent forms, and detailed records of medical device disposition. The investigator will maintain complete, accurate and current study records during the study and for 10 years after the later of the date on which the study is terminated or completed, or the date the records are no longer required.

6 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) may be prepared before database lock. When using the terminology descriptive statistics it means that number of patients, mean, median, standard deviation, minimum and maximum values will be presented for continuous data and frequencies and percentages for categorical data.

If nothing else is stated, descriptive statistics will be given for each variable in the study and p-values may be complemented by confidence intervals as appropriate. All p-values presented will be two-sided. A p-value less than 5% will be called "statistically significant" but all conclusions will be based on the primary objective and hence multiplicity is accounted for even though careful interpretations are necessary as multiple tests are performed.

Analysis populations are defined as follows:

- The Intent-to-Treat (ITT) population includes all enrolled subjects who underwent guided bone regeneration procedure.
- The Per-Protocol (PP) population includes all enrolled subjects who had successful guided bone regeneration procedure and no major protocol deviations (defined as inclusion/exclusion or informed consent violations.)

The ITT population will be the primary analysis population for all endpoints. Analyses on the PP population will be supportive of the ITT analyses.

Demographics and other baseline characteristics

Demographics and other baseline characteristics will be presented by means of descriptive statistics (by group and in total). Continuous variables will be presented by means of number of observations (N), minimum (min), median, maximum (max), mean, and standard deviation (std). Discrete variables will be presented by frequency and percentage.

Covariates and prognostic variables

No covariates are judged to influence the outcome of the primary or any of the secondary variables.

Handling of dropouts and missing data

Patients dropping out from the trial prior to study end will not be replaced. Data totally missing will not be estimated.

Multicenter

This study is a multicenter study. However, there is not a priori reason to suspect that there will be any qualitative differences between the centers regarding any of the efficacy variables nor regarding the safety variables. Therefore, the primary statistical analyses will not include center in the model.

In order to harmonize the use and handling of the graft materials, training will be conducted prior to study start at each center.

Subgroup analyses

No subgroup analyses are planned.

6.2 Method of statistical analysis

Primary objective

The primary objective is to compare dimensional bone changes from baseline (Visit 2) to six months (Visit 7) occurring in a single bound edentulous space following alveolar bone regeneration using three different techniques.

Assume the change (in the mid-buccal horizontal bone dimensions from baseline to six months) is denoted C_A, C_B and C_C, for group A, B and C, respectively. The null-hypotheses (two) is then to test if:

H_0 $C_A = C_i$ (i = B and C, respectively)

can be rejected and hence

H_1 $C_A \neq C_i$ (i = B and C, respectively)

accepted.

H_0 will be tested by means of the Wilcoxon rank sum test. A p-value less than 5% will be regarded statistically significant.

Secondary objectives

Secondary objectives of the study are to evaluate and compare clinical healing parameters between different grafting techniques (i.e. to compare between groups A, B, and C):

- Inflammation by assessing the presence or absence of soft tissue erythema within 3 mm from the crestal incision at 1 week, 2 weeks, 4 weeks, and 6 months following bone augmentation. The chi-squared analysis will be used.
- Infection by determining the presence or absence of suppuration or soft tissue fluctuance at 1 week, 2 weeks, 4 weeks, and 6 months following bone augmentation. The chi-squared analysis will be used.
- Soft tissue complications by determining the presence or absence of membrane exposure or soft tissue dehiscence at 1 week, 2 weeks, 4 weeks, and 6 months following bone augmentation. The chi-squared analysis will be used.

6.3 Determination of sample size

A sample size of 20 participants per treatment group was selected following power calculations and allowing for 10% patient dropout. A sample size of 18 patients was calculated for the primary outcome variable (horizontal bone changes) with the assumption that the detectable difference would amount to 0.5 mm with a standard deviation of 0.5. The type I error probability was set at 0.05 and the statistical power was set at 80%.

6.4 Statistical analyses during the course of the study

The primary and secondary objectives will be analyzed when all data from the 6 month follow-up visit has been collected, entered, verified, and validated (partial clean file).

7 STUDY MANAGEMENT

7.1 Monitoring

A monitoring plan will be developed prior to the initiation of the investigation which outlines the extent and nature of monitoring appropriate for the clinical study, including the frequency of visits, the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical study.

Data will be verified to source during the monitoring process. The Contract Research Organization (CRO), NAMSA will be responsible for monitoring this clinical investigation.

Before first subject into the study, a representative from the CRO will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of the CRO.

During the study, a monitor from the CRO will have regular contact with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm the study team is adhering to the protocol and that data are being accurately recorded in the eCRFs.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (e.g., clinic charts).

The monitor will be available between visits if the investigator(s) or other staff at the center need information and advice.

7.2 Audits and inspections

Authorized representatives of the CRO or IRB may visit the center to perform audits or inspections, including source data verification. The purpose of a CRO audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, applicable Good Clinical Practice (GCP), and 21 CFR Part 50.

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved. New study staff will not perform any study related activities until formal approval from the Principal investigator.

7.4 Changes to the protocol

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to or approved by each IRB.

If a protocol amendment requires a change to a particular center's Informed Consent Form, the center's IRB must be notified. Approval of the revised Informed Consent Form by the IRB is required before the revised form is used.

The sponsor will distribute administrative changes, amendments and new versions of the protocol to each principal investigator.

7.5 Study timetable

Before a subject's enrollment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements
- Approval of the study, investigator, Informed Consent and HIPAA form by the IRB as required
- Collection of study required documents

8 ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by the IRB as appropriate. The investigator must not enroll any subjects into the study until formal written approval is given by the CRO.

The Principal Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study.

Progress reports and notifications of SAEs (and ADEs) will be provided to the IRB according to local regulations and guidelines.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki 2008, Good Clinical Practice (GCP), 21 CFR Part 50 and local IRB requirements.

8.3 Informed consent

The investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Informed consent process will be conducted in accordance with Declaration of Helsinki 2008 and 21 CFR Part 50. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator(s) must store the original, signed Informed Consent Form in the subject's medical record. A copy of the signed Informed Consent Form must be given to the subject.

8.4 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data will be identified by subject ID, study code and initials.

The Informed Consent Form will also explain that for data verification purposes, the CRO may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

9 PROCEDURES IN CASE OF EMERGENCY

9.1 Medical emergency

In the case of a medical emergency you may contact a representative from the study team.

Role in the study	Name	Address & telephone number
Principal Investigators	Lyndon Cooper, DDS, PhD	UNC School of Dentistry 4610 Koury Oral Health Sciences Buildling CB #7450 Chapel Hill, NC 27599-7450 Tel: (919) 537-3175
	Homayoun H. Zadeh, D.D.S., Ph.D.	University of Southern California Ostrow School of Dentistry 925 34th Street Room 4278 Los Angeles, CA 90089-0641 Tel: (213)-740-1415
NAMSA- Medical Research Organization monitoring	Nicole Feist, Sr. Medical Research Manager	NAMSA 4050 Olson Memorial Hwy, Suite 450, Minneapolis, MN 55422 Tel: (612) 787-5386 Fax: (763) 287-3836

9.2 Pregnancy

Many physiologic changes can be observed in the pregnant patient and should be considered when planning dental treatment. It has been suggested to avoid elective dental procedures in the 1st and 3rd trimesters due to risk of spontaneous abortions, pre-term births, increased patient discomfort, and increased likelihood of intraoperative complications (14). The ultimate goal in dental therapy during pregnancy should be to educate the patient on the importance of oral hygiene and plaque control, perform periodontal maintenance therapy and treat emergency situations.

Pregnancy itself is not regarded as an AE/ADE unless there is a suspicion that the medical device under study may have interfered with the effectiveness of a contraceptive medication.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported as SAEs. Elective abortions without complications should not be handled as AEs/ADEs.

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