TWO-ARM, SINGLE BLIND, RANDOMIZED POST-MARKET STUDY ON THE USE OF HEALICOIL™ REGENESORB SUTURE ANCHOR IN THE REPAIR OF TEARS OF THE ROTATOR CUFF

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Study Product Name:	HEALICOIL REGENESORB Suture Anchor Smith & Nephew, Inc. 150 Minuteman Rd Andover, MA 01810
Primary Investigator:	Stefan Tolan, MD

Protocol Summary

Title of Study:	Two-Arm, Single Blind, Randomized Post-Market Study on the use of HEALICOIL™ REGENESORB Suture Anchor in the repair of tears of the rotator cuff
Study Type:	Postmarket
Primary Investigator:	Stefan Tolan, MD
Primary Endpoint:	85% high quality ossification at anchor site for HEALICOIL REGENESORB and 49.9% high quality ossification for TWINFIX Ultra HA at 24M
Secondary Endpoints:	Repair success rate (Defined as subjects without a re-tear or re-intervention) between groups, Pain/Function (VAS, WORC, PENN, SANE, EQ-5D, ROM), Patient Satisfaction, Difference in complication rates between groups
Design:	Prospective, randomized, two-arm, single-blind study
Length of Study:	24M follow-up
Sample Size:	68 subjects

Schedule of Events

	BL	Proc	6WK	6M	12M	24M
Informed Consent	√	-	-	-	-	-
Inclusion/Exclusion	√	-	-	-	-	-
Demographics/Medical History	√	-	-	-	-	-
Surgical Details	-	√	-	-	-	-
Physical Exam-ROM	√	-	√	√[1]	-	√
Visual Analogue Scale (VAS)	√	-	√	√	√	√
PENN	√	-	√	√	√	√
WORC	√	-	√	√	√	√
SANE	√	-	√	√	√	√
EQ-5D	√	-	√	√	√	√
Ultrasound	-	-	-	√[2]	-	-
MRI	-	-	√	-	-	-
CT Scan	-	-	-	-	-	√
Patient Satisfaction	-	-	√	√	√	√

Adverse Event Assessment	-	√	√	√	√	√
End of Study/Exit	*	*	*	*	*	*

[1]Physical Exam at 6M will occur at the same visit as the 6+ month ultrasound.
[2]Ultrasound will be done at ≥ 6 months post-procedure.
* End of Study will be noted on study spreadsheet at any point throughout the trial.

1. Background and Information

Rotator cuff disease is the most common cause of shoulder pain, and as the aging population is increasingly active and less willing to accept functional limitations, the incidence of this disease is expected to grow (Gomoll 2004, Coghlan 2008). While a large proportion of patients presenting with rotator cuff disease are asymptomatic, research has shown that over 50% of individuals with asymptomatic rotator cuff tears will develop pain over an average of 2.8 years (Yamaguchi 2001). Although not life-threatening, a rotator cuff tear can cause significant pain, weakness, and limitation of motion (Crusher 2000). Once a tear occurs, it is unlikely to heal without treatment, and left untreated, large tears may result in chronically retracted muscle-tendon units that undergo fatty degeneration resulting in weakness, a potentially irreversible process (Fukuda 2003, Gomoll 2004). Thus, once a tendon ruptures, the primary method of repair is surgical intervention, focusing on the re-establishment of the interface between the tendon and bone. Tendons are typically very slow to heal, and as such, prolonged immobilization and lengthy rehabilitation are required. An effective treatment that shortens the duration of symptoms and disability has the potential to be of significant value in terms of reduced morbidity and costs to both the individual and the community (Coghlan 2008).

Standard treatment of full thickness rotator cuff repairs involves tissue reattachment. This can be accomplished by various techniques, with the gold standard being suture anchors plus suture fixation. First generation suture anchors were made of metal and were initially well received- reporting pull out strengths rivaling that of other suturing techniques, however, reports of loosening, migration, chondral injury, revision surgery, and magnetic resonance imaging interference has led device makers to explore other materials. The desire for a high strength anchor without the issues that metallic anchors presented has led to the creation of plastic and bioabsorbable suture anchors. PEEK, for instance, is not biodegradable but is radiolucent, allowing good post- operative imaging. As a plastic, it also affords solid fixation strength yet remains soft enough for a revision surgery drill through. These characteristics have made PEEK anchors popular, emerging in numerous designs and indications.

The advantage of bioabsorbable material over its plastic (such as PEEK) counterpart is it allows for the restoration of natural anatomy as it resorbs, which in turn eases revisions as there is no need to drill through an existing anchor. Bioabsorbables include a wide array of materials composed of natural, synthetic, or biosynthetic polymers. There are more than forty types of polymers that have been developed for use in surgery. More widely known types of these polymers are polyglycolic acid (PGA) and polylactic acid (PLA), along with their many variations. The poly-l-lactic acid (PLLA) variation was once considered the gold standard of bioabsorbable materials, however; clinical information and animal studies have since demonstrated that the degradation properties of PLLA are slow, taking as many as five to seven years to degrade with no evidence of replacement by bone. Instead, replacement by fibrous or fatty-fibrous tissue has been seen. Because of these limitations, composite materials consisting of polymer and ceramic blends are emerging as materials for suture anchors. Bioactive ceramics are known to be osteoconductive on their own and have been clinically proven for use as bone graft substitutes. Utilization of the appropriate polymer variation is thought to increase the likelihood of maintaining mechanical strength through the healing period while subsequently assuring timely degradation to avoid the complications seen in the long term absorbable implants.

Despite the developments in suture anchor technology, concern remains about how well the rotator cuff heals back to the insertion site after repair. Clinical studies have shown the rate of radiographic failures at the repair site to occur anywhere from 11% to 95% of patients (Fealy 2006, Galatz 2004, Harryman 1991, Lafosse 2007, Gerber 2000, Boileau 2005). Patients who fail to heal or who re-tear may still experience pain relief, although they have inferior functional results compared with patients

whose repairs have healed (Galatz 2004, Harryman 1991). In an effort to minimize failures, stronger sutures and new repair techniques have been developed in an attempt to improve biomechanical strength (Lafosse 2007). In spite of these new techniques, approximately 20% of patients fail to heal or experienced a re-tear (Slabaugh, 2010). Smith & Nephew has designed a bioabsorbable suture anchor that, due to its design, maybe impact healing at the tendon- bone interface.

In a pre-clinical ovine study, HEALICOIL™ REGENESORB demonstrated osteointegration beginning at 12 weeks post-implantation. This study will seek to replicate these findings in humans. Magnetic resonance images (MRIs) at an early time point will be used to show the screws in contrast to bone and soft tissues, enabling the radiologist to provide screw measurement and determine percent bony ingrowth. The CT at 24 months should allow for a more drastic transition to the cortical-like bone making the bone to remnant anchor material more apparent.

2. Study Design

This is a prospective, randomized, two-arm study to assess the outcomes of the HEALICOIL REGENESORB suture anchor compared to the TWINFIX™ Ultra HA suture anchor when used in rotator cuff repair. A total of 68 subjects will be enrolled at the research site.

3. Study Objectives

The purpose of this study is to compare the clinical and radiographical outcomes of HEALICOIL REGENESORB suture anchor (open design) vs. TWINFIX Ultra HA suture anchor (closed design) in patients requiring rotator cuff repair.

3.1. Study Endpoints

3.1.1. Primary Endpoint

85% high quality ossification at anchor site for HEALICOIL REGENESORB and 49.9% high quality ossification for TWINFIX Ultra HA at 24M

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3.1.2. Secondary Endpoints

- Repair success rate (Defined as subjects without a re-tear or re-intervention) between groups as determined by ultrasound
- Difference in pain/function from baseline on the following:
    - Visual analog scale (VAS) pain score,
    - Western Ontario for Rotator Cuffs (WORC)
    - PENN Shoulder Score (PENN)
    - Single Assessment Numeric Evaluation (SANE)
    - EQ-5D
    - Range of motion (ROM).
- Patient Satisfaction

3.1.3. Safety Endpoints:

- Adverse Events
- Difference in complication rates between groups

4. Study Material

The Smith & Nephew HEALICOIL REGENESORB Preloaded Suture Anchors consist of an absorbable suture anchor with an attached non-absorbable suture assembled to an insertion device. The suture anchors are intended to provide secure reattachment of soft tissue to bone.

5. Control Device

The control device selected for this study is the TWINFIX™ Ultra HA suture anchor, which is approved for use in rotator cuff repair.

6. Study Population

This clinical study of the HEALICOIL™ REGENESORB suture anchor can fulfill its objectives only if appropriate subjects are enrolled. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable. The subject recruitment period will continue until the study enrollment limit of 68 subjects is reached.

6.1. Subject Recruitment and Screening

6.1.1. Screening

Patients who present with the need for rotator cuff repair will be screened for inclusion into the study. Following discussion of the study between the patient and the treating physician, the patient will be given the opportunity to move forward with the informed consent process.

6.1.2. Enrollment

The subject will be considered enrolled once voluntary informed consent has been given, and the form has been signed and dated by all required parties.

6.1.3. Randomization

Subjects will be randomized to a treatment arm using a 1:1 ratio. Once study eligibility has been confirmed, the study coordinator or designee will randomize the subject to a treatment arm. The treatment for each subject will be assigned through the study database.

6.1.3.1. Blinding

Study subjects and radiologists performing MRI and CT analysis will be blinded to the treatment assignment for the duration of the study to reduce the risk of bias.

6.1.4. Subject Identification

All subjects will be assigned a subject identification number to identify the subject on all study-related documents in order to maintain subject anonymity. Subject ID will be assigned at the time of enrollment.

6.2. Subject Inclusion Criteria

Subjects must meet all of the following characteristics for inclusion in the study.

- Male or female, aged 35 to 75 years at the time of surgery.
- Willing and able to give voluntary informed consent to participate in this investigation.
- Full thickness tear of the rotator cuff
- Tear requires repair within one year of initial diagnosis.
- Tear must be anatomically repairable (must be able to get tendon back to the medial position on the footprint and at least back to the tuberosity).

- Willing and able, in the opinion of the Investigator, to cooperate with study procedures, and willing to return to study site for all required post-operative study visits.

6.3. Subject Exclusion Criteria

Subjects with any of the following characteristics must be excluded from participation in the study.

- Evidence of acute trauma including fracture or dislocation of the shoulder joint.
- Chronic retraction.
- Evidence of active infection, osteomyelitis, sepsis or distant infection, which could spread to the index joint.
- Subject has had previous rotator cuff, arthroplasty or fracture procedures on the operative shoulder.
- Subject has had acromioplasty or diagnostic arthroscopy on the operative shoulder within one (1) year prior to scheduled surgery date.
- Evidence of osteomalacia or other metabolic bone disorder(s), which may impair bone or soft tissue function.
- Evidence of other significant shoulder pathology including (Type II-IV lesion, Bankart lesion, Hill Sachs lesion).
- Patient has grade 4 changes to articular cartilage in operative shoulder
- Inflammatory arthropathies.
- Significant muscle paralysis of the shoulder girdle.
- Painful pathologies of the cervical spine.
- Comminuted bone surface, which would compromise secure anchor fixation.
- Non-surgical rotator cuff associated treatment, such as corticosteroid injection, within one (1) month prior to scheduled surgery date.
- Participating in another investigational trial or ongoing study that would interfere with the assessment of the primary and secondary outcomes.
- Female patient who is pregnant, nursing, or of childbearing potential while not practicing effective contraceptive methods.
- Major psychiatric illness, developmental handicap or inability to read and understand the English language.
- Major medical illness that would preclude undergoing surgery.
- Known to be involved in any active injury litigation claims relating to the study shoulder.
- Unwilling or unable to be assessed according to study protocol for two years following surgery.
- Patient requires a concomitant SLAP repair procedure in operative shoulder.
- Surgeon plans to use a Platelet Rich Plasma product or another therapy intended to augment healing of the rotator cuff in the study procedure.
- Protocol specified surgical technique cannot be followed for this subject.
- Rotator cuff repair will be done via open (as opposed to arthroscopic) procedure.

- Any other reason (in the judgment of the investigator).

6.4. Withdrawal of Subjects from Study

All reasonable efforts should be made to retain the subjects for the duration of this study. Once a subject has been withdrawn from the study (pre-maturely or at completion of the study), the study termination form should be completed.

6.4.1. Voluntary Withdrawal by Subject

Study participation is voluntary and subjects may withdraw at any point during the study. If a subject withdraws from the study, the investigator will make all reasonable efforts to determine the reason for the subject's withdrawal and will document the reason on the applicable form. After a subject withdraws from the study, no effort will be made to replace or follow the subject.

6.4.2. Withdrawal by Investigator

The investigator may withdraw subjects from the study for many reasons, including but not limited to the following:

- Occurrence of a serious adverse event
- Investigator's discretion to withdraw subject for safety reasons
- Subject noncompliance with visits and/or assessments
- Subject is lost to follow-up (as defined per section 6.4.3)

6.4.3. Lost to Follow-Up

Subjects will be defined as lost to follow-up when the following procedures have been documented in the subject's source documentation and End of Study CRF:

- At least 2 phone calls made on separate dates to the subject are not returned
- A certified letter is sent to the subject's last known address and the subject does not reply after 30 days

6.4.4. Documentation of Study Completion Status

The completion status of the subject (e.g. completed per protocol, subject withdrawal, device removed, death, lost-to-follow-up, or other reason) should be recorded and the reason for withdrawal, if applicable, should be documented in the source documentation.

7. Informed Consent

Investigators are responsible for obtaining and documenting the voluntary informed consent of the study subjects prior to conducting any study-related assessments per 21 CFR Part 50. The informed consent form should include all elements noted in 21 CFR Part 50 Subpart B and Good Clinical Practice (GCP) guidelines.

In obtaining informed consent investigators must adhere to 21 CFR Part 50 and GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to beginning the trial the investigator must obtain written and dated approval of the informed consent form. Subjects will receive a copy of the initial signed and dated informed consent form prior to the subjects' participation in the trial and any revised informed consent forms during the duration of the trial.

The subject must sign and date the consent form in the presence of the investigator or the investigator's designee, who must sign and date the consent form in the presence of the subject.

The informed consent form and any other written information provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's continued consent. All revised informed consent forms must have written and dated IRB approval in advance of use.

The communications with the subject regarding informed consent process (initial and subsequent) should be documented in the medical record.

8. Study Procedures

8.1. Prior to Study Initiation

The investigator must ensure the activities below are completed prior to initiating the study.

8.1.1. IRB Approval

The protocol and informed consent materials must be approved by the IRB prior to patient enrollment.

8.1.2. Documentation of Qualifications

A current, signed, dated CV and a current medical license for the principal investigator and sub-investigators must be available prior to the study start.

8.1.3. Sponsor Site Initiation

A site initiation meeting with the sponsor and the site must be completed prior to initiating study activities and the site must have written approval from the sponsor to initiate the study.

8.2. Study Assessments

8.2.1. Visit 1- Baseline Assessment

The following information will be collected prior to the study procedure:

- Informed Consent
- Medical History & Demographics: Record general subject medical history and demographics.
- Patient Outcomes: Subject to complete VAS, WORC, SANE and PENN scales
- Range of Motion Assessment

8.2.2. Visit 2- Procedure

The following information will be collected at this visit:

- Surgical Information
- Device Details: Be sure to keep stickers from the device packaging and record device details in the patient medical record and the Operative source documentation form.
- Adverse Events: Record any adverse events experienced by the patient

8.2.3. Follow-Up Visits (6WK, 6M, 12M, 24M)

The following information will be collected at each follow-up visit:

- Patient Outcomes: Subject to complete VAS, WORC, SANE and PENN scales
- Range of Motion Assessment (6WK, 6M+, 24M)
- Patient Satisfaction
- US at ≥ 6M only
- MRI at 6 WK only
- CT Scan at 24M only

8.2.4. Rehabilitation Protocol

Each patient will be given a standardized rehabilitation protocol, which should be followed.

8.2.5. Radiological Procedures

All enrolled patients will receive one CT scan over the course of their study participation. All CT Scans will be conducted utilizing the CT Protocol. Data will be captured on the CT Evaluation Form.

8.2.6. Additional Visits

Additional visits will not be recorded, unless they are due to an adverse event. In this case, an Adverse Event form should be completed.

Table 1: Schedule of Events

	BL	Proc	6WK	6M	12M	24M
Informed Consent	√	-	-	-	-	-
Inclusion/Exclusion	√	-	-	-	-	-
Demographics/Medical History	√	-	-	-	-	-
Surgical Details	-	√	-	-	-	-
Physical Exam-ROM	√	-	√	√[1]	-	√
Visual Analogue Scale (VAS)	√	-	√	√	√	√
PENN	√	-	√	√	√	√
WORC	√	-	√	√	√	√
SANE	√	-	√	√	√	√
EQ-5D	√	-	√	√	√	√
Ultrasound	-	-	-	√[1]	-	-
MRI	-	-	√	-	-	-
CT Scan	-	-	-	-	-	√
Patient Satisfaction	-	-	√	√	√	√
Adverse Event Assessment	-	√	√	√	√	√
End of Study/Exit	*	*	*	*	*	*

[1] Ultrasound will be done at ≥ 6 months post-procedure.

* End of Study will be noted on study spreadsheet at any point throughout the trial.

9. Risk Analysis

9.1. Manner in Which Potential Risks Will Be Minimized

The investigators have proper experience and training to support the use of the current device. The investigators in this study have extensive experience in rotator cuff repair.

Careful attention to subject selection criteria and surgical techniques may reduce the potential of any adverse effects.

Potential risks associated with suture anchors are the following:

- Mild inflammatory reaction
- Foreign body reaction
- Infection, both deep and superficial
- Allergic reaction

9.2. Potential Benefits

Participation in this study may offer no benefit to subjects. However, it is possible that the use of HEALICOIL™ REGENESORB suture anchors could lead to improved tendon to bone repair.

10. Adverse Events

10.1. Definitions

An adverse event is defined as any untoward medical occurrence in a clinical investigation in which a subject is administered a study device and which does not necessarily have a causal relationship with the device. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or an abnormal radiographic finding), symptom, or disease temporally associated with the use of study device, whether or not related to the study device. The following are specific definitions of adverse events:

Adverse Event (AE) — any untoward medical occurrence in a subject, regardless if there is a relationship between the AE and the device.

Serious Adverse Event (SAE) — an adverse event that:

- leads to a death
- leads to a serious deterioration in the health of a subject that results in a life-threatening illness or injury
- results in a permanent impairment of a body structure or a body function
- requires in-subject hospitalization or prolongation of existing hospitalization
- results in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- results in congenital anomaly/birth defect

Adverse Device Effect (ADE) — any untoward and unintended response to a medical device (This definition includes any event that is a result of a user error).

Unanticipated Adverse Device Effect (UADE) — An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with this device that was not previously identified in nature, severity, or degree of incidence in the application of the device.

Device related adverse events can include any of the following:

- Any device implant component failure (e.g. breakage)
- Any device component experiencing dislocation, subluxation, subsidence, or migration.
- Unintended bone fractures.
- Nerve damage (as evidenced intra-operative or immediate postoperative by motor and/or sensory deficit not present preoperatively).
- Other adverse events as listed in the Risk Analysis section (9.0) that are deemed device related and serious.

10.2. Treatment for Adverse Events

In the event of an adverse event, the investigator and/or other professional personnel in attendance will provide whatever appropriate medical treatment is indicated for the problem.

10.3. Documentation of Adverse Events

All adverse events will be documented in the source documentation. Beginning after the study procedure has taken place, all AE's, including those measured, observed or volunteered, will be recorded on the applicable case report form. The investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event being reported. The investigator will then record all relevant information regarding an AE onto the study CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs and symptoms.

When reporting an AE, the investigator will evaluate the event for duration, intensity, relationship and outcome.

Examples of an AE:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition.
- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- A new condition detected or diagnosed after study device administration even though it may have been present prior to the start of the study.
- Pre- or post-procedure events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a subject's previous treatment regimen).

An AE Does NOT Include:

- Medical or surgical procedures. The medical condition that leads to the procedure is the AE.

- Hospital admissions where an untoward medical occurrence did not occur.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- The condition/indication being studied or expected progression, signs, or symptoms of the condition/indication being studied unless more severe than expected for the subject's condition.
- Post-operative findings of swelling or pain within two (2) weeks of the initial procedure, unless deemed by the physician as of greater severity than expected.

10.4. Follow-Up of Adverse Events

After the initial AE report, the investigator is required to proactively follow each subject until the event resolves. All AEs documented at a previous visit that are designated as ongoing will be reviewed at subsequent visits/contacts.

Adverse events will be followed until resolution, until no further changes in the event are expected (i.e. the point at which a subject experiencing a critical adverse event is treated successfully and stabilized even though he/she may continue to experience lingering sequelae that may never resolve), until the subject is lost to follow-up, or until it is agreed that further follow-up of the event is not warranted (e.g. non-serious, study therapy unrelated, mild or moderate adverse events ongoing at the subject's final study visit).

New or updated information shall be recorded by completing an AE follow-up CRF.

11. Reporting of Adverse Events

11.1. Investigator Adverse Event Reports

Investigators are responsible for reviewing all SAEs, ADEs, SADEs, and UADEs, determining the relationship to the device and documenting on the appropriate CRF. All SAEs, ADEs, SADEs and UADEs must be reported by the investigator to the IRB (as applicable) as soon as possible but no later than ten (10) working days after learning of the event. The investigator must submit a detailed report that will identify the description of symptoms, classification of the event, date of onset, severity, treatment, and outcome. Supporting medical records may be obtained as an adjunct to an adverse event report and placed in the subject's study file.

All AEs will be categorized as mild, moderate or severe based on the following definitions:

Mild: The subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or wellbeing.

Moderate: The subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or wellbeing and may require medical intervention and/or close follow-up.

Severe: The adverse event interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or wellbeing. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

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12. Source Documentation

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject and each assessment in the protocol (source documents). Source documents include all information in original records and certified copies of original records of clinic findings, observations or other activities in the study necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (e.g., hospital records, clinic and office charts, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection and shipment records, research subject files, etc.)

13. Disclosure of Data and Data Security

13.1. Data Security and Confidentiality

The clinical data obtained in this study will be kept private. In any sort of published report, there will be no identifying information. Records for this study may be reviewed by the IRB and/or other government agencies may inspect and photocopy all medical records applicable to involvement in this study.

Participating subjects will be asked to sign a consent form that includes an authorization to use and/or disclose personal health information. Subjects are free to refuse authorization to transfer personal information. If the subject chooses not to agree to this authorization, the subject is not eligible to participate in the study. Personal information (including sensitive personal health information, such as medical history) if relevant to the study will be reviewed, collected in a computer database, stored in electronic or manual files, audited, and / or otherwise processed by the investigator, regulatory agencies, and other persons and/or agencies as required by law or allowed by applicable regulations.

14. Statistical Procedures

To determine sample size, we have powered our study (a-priori) using test of proportions, assuming inequality, with two independent groups. The primary outcome measure used will be an ossification quality score at 24 months. The ossification quality score is an ordinal measure of quality of bone reabsorption that is divided into four progressive groups. Quality score 1 reflects “little or no bone ossification”, Quality score 2 reflects “Some ossification; discontinuous or with a wide lucent rim”, Quality score 3 reflects “Ossification with a thin lucent rim”, and Quality score 4 reflects “Good ossification; border of tract vague”. For this study, Quality scores 1 and 2 will be merged (defined as low quality ossification) as will Quality scores 3 and 4 (defined as high quality ossification).

For a conservative 85% proportional Quality score measures of 3 and 4 (high qualify ossification) for the HEALICOIL™ REGENESORB group and a 49.9% proportional Quality score measures of 3 and 4 (high qualify ossification) for the TWINFIX™ Ultra HA group (Barber, Dockery and Cowden. Arthro. 2013).

A two group chi-square test with a 0.050 two-sided significance level will have 80% power to detect the difference between a Group 1 proportion, π_1, of 0.499 and a Group 2 proportion, π_2, of 0.850 (odds ratio of 5.689) when the sample size in each group is 27 subjects by end of 24 months. Since a drop-out rate of 20% is expected from baseline, we will target total of 68 subjects to meet the time-oriented goals of the analyses.

The TWINFIX Ultra HA differs from the reference device (Healix BR, DePuy Mitek) in material properties and characteristics. TWINFIX Ultra HA is composed of a Poly-L-Lactide/Hydroxyapatite

(PLLA/HA) blend while the reference device is a poly-l-lactideco-glycolide-β-tricalcium phosphate and calcium sulfate (PLLA/PGA-β-TCP, Ca So4) blend. Based on our pre-clinical testing the PLLA/HA device takes longer to degrade when compared to a device composed of PLLA/PGA. We therefore predict that our control device (TWINFIX) will not meet the hypothesized proportional score of 49.9%.

15. Investigator Responsibilities

15.1. Medical Oversight

At all times the investigator is responsible for the rights, safety and welfare of subjects under the investigator's care. The investigator is directly responsible for the ongoing medical care of subjects enrolled in this study, as well as for all study-related medical decisions. During and following a subject's participation in the study, the investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values if applicable, related to the trial. The investigator should inform the subject when medical care is needed for all intercurrent illness(es) of which the investigator becomes aware. The investigator should inform the subject's primary physician about the subject's participation in the study, if the patient has a primary physician and if the subject agrees to the primary physician being informed.

15.2. Investigator Records

The Investigator will maintain complete, accurate and current study records, including but not limited to the following materials:

1. Correspondence with other Investigators or the IRB;
2. Study Subject Records including signed and dated informed consent forms, all source documentation, subject CRFs, queries and records of exposure of each subject to the device;
3. All relevant observations, including records and reports concerning adverse effects (whether anticipated or unanticipated);
4. Current study protocol
5. The approved blank Informed Consent form and blank Subject CRFs;
6. Certification that the Investigational Plan has been approved by all of the necessary approving authorities; and
7. Signed/dated current CV's of the Principal Investigator and any participating Co-Investigators.

16. Bibliography

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