Protocol DVAL24003-P

A Pilot Clinical Study to Evidence Safety and Efficacy of Fracture Fixation of the Distal Radius using a Bioresorbable Bone Adhesive to Augment Metal Hardware

Version 3.0

September 25, 2025

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SYNOPSIS

Study Title:	A Pilot Clinical Study to Evidence Safety and Efficacy of Extremity Fracture Fixation of Distal Radius Fractures using a Bioresorbable Bone Adhesive to Augment Metal Hardware
Protocol Number:	DVAL24003-P
Study Registration:	This protocol will be registered in the clinicaltrials.gov database before enrollment begins.
Aim:	The aim of this Pilot Study is to demonstrate the safety and efficacy of the use of Tetranite® Bone Adhesive for Extremity Fracture Fixation (TN-MFF) to augment hardware fixation of complete articular distal radius fractures treated surgically by open reduced rigid internal fixation using a volar approach procedure.
Primary Endpoints:	The primary endpoints will be the following: • Safety based on the rate of serious device related adverse events. • Efficacy based on the following radiographic, clinical, and functional evaluations: ○ Fracture union assessment at the 26-week follow-up ○ DASH assessment at the 26-week timepoint
Secondary Endpoints:	The following secondary endpoints will be assessed: • Grip strength compared to baseline (contralateral limb) • Range of motion compared to baseline (contralateral limb) • Patient reported outcome measures (SF-36, DASH, VAS Pain Scores) • Maintenance of reduction compared to baseline (surgery) • Fracture union assessment at the 6-,12-week follow-ups
Tertiary Endpoints:	• Clinical CT to confirm healing, measure calcification, and record bone mineral density • Clinical assessment of the fractured limb
Primary Analysis:	The primary analysis will be conducted 26 weeks after the fracture repair surgery by determination of the following success criteria for the following primary endpoints: • Demonstration that TN-MFF can be safely used in patients as evidenced by the rate serious device related adverse events from the time of fixation to 26 weeks post-procedure. • DASH scores decrease at 26 weeks relative to baseline (screening) • Fracture union is achieved in at least 85% of patients by 26 weeks.
Study Design:	A prospective, multi-center (up to 4 sites), single-arm, study of 20 subjects. Patient enrollment will consist of subjects with an AO/OTA type 2R3C distal radius fracture. Enrollment will be prospectively stratified based on patient age (Stratum A: <65 and Stratum B: ≥65 years)
Number of Subjects:	20 subjects
Subject Population:	Subjects must be greater than 21 years of age or older who require surgical intervention for a **distal radius** (AO/OTA type 2R3C) fracture and who meet all the Inclusion/Exclusion criteria listed below.

Inclusion Criteria:	**<u>Screening Inclusion Criteria:</u>** • Unilateral, unstable and/or displaced **distal radius** AO/OTA type 2R3C fracture. • Standard treatment would consist of open reduction internal fixation (ORIF) with plate(s) and screws using a volar approach • Surgical visit occurs within 2 weeks of injury. • No radiographic evidence of fracture healing prior to surgical treatment. • Male or female, greater than 21 years of age • Subject living independently and ambulatory at the time of injury. • Subject, and/or subject's representatives are able and willing to provide informed consent and HIPAA authorization. • Subject able and willing to meet all study requirements, including attending all post-index procedure assessment visits and radiological tests. **<u>Intra-Operative Inclusion Criteria</u>** • No sign of active infection at the planned operative site. • Surgeons will decide whether the fracture site is a good candidate for TN-MFF use once the site is open and they can visualize the bone and surrounding soft tissue.
Exclusion Criteria:	• Significant ligamentous disruption requiring independent repair • Other fractures of the carpal bones or injured limb (Note: an associated ulnar styloid fracture is not exclusionary) • Pathological fracture related to an underlying malignancy • Open fractures • A previous fracture in the injured bone within the last 12 months • Presence of other orthopaedic implant in the injured bone • Patients with presumptive diagnosis of named nerve or blood vessel injury • Current infection (either superficial or deep) at the planned operative site • Sepsis within one week from the planned index procedure • History of radiotherapy to the area • Active chemotherapy treatment • Patients receiving treatment with biologics for systemic inflammatory disease (e.g., Enbrel) • Physically or mentally compromised and unable to provide consent or perform functional examinations • Subject has a condition with anticipated survival shorter than 12 months

Treatment Plan for the Study Subjects:	**Visit**	**#**	**Procedures**	**Schedule**
	Screening	1	Informed Consent, Inclusion/Exclusion Determination, Demographics, Pregnancy Test, Review of Medical History, Imaging: CT (pre-op) & X-Ray, PROMS, Clinical Assessment	
	Surgery	2	Inclusion/Exclusion Determination, Intra-operative eligibility, Assessment of Adverse Events, Surgery, Imaging: CT (post-op) & X-Ray	≤ 2 weeks from injury
	Postoperative Follow-up 1	3	Assessment of Adverse Events, Imaging: X-Ray, PROMs, Range of Motion, Clinical Assessment	2 weeks (+7/-3) days from surgery
	Postoperative Follow-up 2	4	Assessment of Adverse Events, Imaging: X-Ray, Grip Strength, PROMs, Fracture Union, Range of Motion, Clinical Assessment	6 weeks (± 7) days from surgery
	Postoperative Follow-up 3	5	Assessment of Adverse Events, Imaging: X-Ray, Grip Strength, Fracture Union, PROMs, Range of Motion, Clinical Assessment	12 weeks (± 14) days from surgery
	Postoperative Follow-up 4	6	Assessment of Adverse Events, Imaging: CT & X-Ray, Grip Strength, Fracture Union, PROMs, Range of Motion, Clinical Assessment	26 weeks (± 30) days from surgery
	Postoperative Follow-up 5	7	Assessment of Adverse Events, Imaging: X-Ray, Grip Strength, PROMs, Range of Motion, Clinical Assessment *Fracture Union (optional) – based on 26-week radiologist review*	52 weeks (± 60) days from surgery
Study Products:	Tetranite Bone Adhesive for Extremity Fracture Fixation, TN-MFF			
Registration Status:	TN-MFF is the experimental device under study.			
Safety:	Study subjects will be monitored for all adverse effects during the scheduled examinations and at any examinations resulting from study subjects' self-reported concerns. A licensed physician will evaluate any evidence of systemic adverse effects. Two independent musculoskeletal radiologists will evaluate radiographs for maintenance of reduction and fracture union with a third musculoskeletal radiologist to adjudicate differences.			
Countries in which the Study will be Conducted:	United States			

Number of Participating Centers:	Up to four (4) sites will be established for this study.
Study Monitor:	Sarah Moss Clinical Research Manager Prime Path Medtech 1321 Upland Dr Suite 6792 Houston, TX 77043 USA smoss@primepathmedtech.com
Principal Investigator at Centers:	Site 1: Cambridge Health Alliance Hans Van Lancker, MD, Chief of Orthopaedics 1493 Cambridge St., Cambridge, MA 02139 Site 2: TBD TBD Site 3: TBD TBD Site 4: TBD TBD
Estimated Date of Study Initiation:	Q3 2025
Estimated Date of Study Completion:	Primary Endpoint (26-weeks): Q4 2026 Final Follow up (52-weeks): Q2 2027
Sponsor:	RevBio, Inc.
Compliance:	This study and any amendments will be performed according to ISO 14155:2020, ICH E6(R3) Guideline on Good Clinical Practice (GCP 2025) and conformed to the Declaration of Helsinki (last revised Fortaleza 2013). Local legal and regulatory requirements include compliance with 21 CFR 812, 21 CFR 820, 21 CFR 50, 21 CFR 54, and 21 CFR 56.

Schedule of Procedures / Assessments

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening Visit	**Surgery** ≤ 2 weeks from injury	**2wk Post-Op Evaluation** 2 weeks (+7/- 3)	**6wk Post-Op Evaluation** 6 weeks (± 7) days from surgery	**12wk Post-Op Evaluation** 12 weeks (± 14) days from surgery	**26wk Post-Op Evaluation** 26 weeks (± 30) days from surgery	**52wk Post-Op Evaluation** 52 weeks (± 60) days from surgery
Signed Informed Consent Form	X						
Inclusion and Exclusion Determination	X	X					
Demographics	X						
Pregnancy Test	X[1]						
Review of Medical History	X						
Surgery: ORIF		X					
Intra-operative eligibility		X					
Assessment of Adverse Events		X	X	X	X	X	X
Imaging: CT[3]	(X)[4]	X				X	
Imaging: X-Ray	X	X	X	X	X	X	(X)[2]
Grip Strength				X	X	X	X
PROMs: DASH, SF-36 and VAS	X		X	X	X	X	X
Radiographs for Fracture Union Assessment				X	X	X	(X)[2]
Range of Motion Assessment			X	X	X	X	X
Clinical Assessment	X		X	X	X	X	X

[1] The pregnancy test must be administered per hospital policies and occur prior to TN-MFF implantation.

[2] The need for a Fracture Union and X-Rays will be based on assessment of fracture union at the 26-week post-op evaluation.

[3] If additional imaging is medically required at any other timepoints, it will be included in the study file for the subject.

[4] Pre-operative CT scans are typically standard of care for intra-articular distal radius fractures and will be included in the study file for the subject but would not be used for analysis of outcome measures

Contents

1. BACKGROUND AND RATIONALE

In the U.S., about 6.3 million people experience a fracture each year and the majority of these fractures occur in the extremities. Fractures, often resulting from falls, sports injuries, or motor vehicle accidents affect all ages, but the elderly are at an increased risk due to poor bone quality. The number of fragility fractures are expected to double or triple by 2040 as the population ages with distal radius fractures making up approximately 18% of fractures in the elderly population.[1,2,3]

Distal radius fractures are typically treated through nonoperative closed reduction (casting), open reduction internal fixation with plates and screws, or external fixation with percutaneous pinning techniques.[4] Practice guidelines for distal radius fractures was approved by the American Academy of Orthopaedic Surgeons in 2009, which recommends surgical fixation rather than cast fixation for fractures with significant radial shortening (> 3 mm), dorsal tilt (> 10 °), or intra-articular displacement or step-off (> 2 mm). Complete articular distal radius fractures (AO/OTA fracture type C) present challenges for surgeons to fixate bone fragments and achieve anatomical reduction despite advances in surgical technique and implant design. Nonunion, malunion, loss of mobility, and hardware failure continue to remain a significant cause of revision surgery with reported complication rates up to 10% for surgically treated distal fractures with significantly high prevalence for AO/OTA type C fractures.[3,5]

To address this problem, RevBio developed Tetranite® Bone Adhesive for Extremity Fracture Fixation (TN-MFF), a novel bone adhesive that can fill gaps in bone, fixate bone fragments, and accelerate healing through its osteoconductive effects. TN-MFF can be used as an adjunct to traditional hardware fixation to provide immediate load sharing between the metal plate and screw systems, and bone. It provides additional stability by enhancing fracture stabilization to achieve better healing and prevent hardware failure.

The product contains a radiocontrast agent, barium sulfate, for visualization during intra-operative imaging and post-operative follow-up assessments. TN-MFF has been shown to be resorbed and replaced with new bone over the course of 6-12 months in a pre-clinical pivotal animal study through high resolution CT and histological examinations. Radiographic assessments from this study using X-Rays concluded that residual contrast agent may be remaining in the defect site following the resorption of TN-MFF and replacement with new bone along the fracture gap.

2. STUDY OBJECTIVES AND ENDPOINTS

The objective of this study is to show evidence of safety and efficacy for the use of TN-MFF as a bone adhesive when used to augment metal hardware fixation of distal radius fractures. Upon IDE-Approval to initiate human studies, RevBio will provide product training to clinical investigators to initiate a multi-site clinical trial according to ISO and FDA standards.

2.1 Study Objectives

2.1.1 Primary Objectives:

Assess the safety and efficacy of the use of Tetranite for Extremity Fracture Fixation (TN-MFF) in a clinical trial to allow for an expanded, controlled, pivotal clinical study in a greater number of patients.

2.1.2 Secondary Objectives:

Assess the efficacy and clinical use of the use of Tetranite for Extremity Fracture Fixation (TN-MFF) to establish outcome measures for the controlled, pivotal clinical study in a greater number of patients.

2.2 Primary Endpoints

The primary endpoints will be the following:

- Safety based on the rate of serious device related adverse events for up to the 26-week postoperative time point.
- Efficacy based on the following radiographic, clinical, and functional evaluations:
    - Fracture union assessment at the 26-week follow-up
    - DASH assessment at the 26-week timepoint to assess clinical and functional outcomes compared to baseline (screening).

2.3 Secondary Endpoints

The following secondary endpoints will be assessed:

- Grip strength compared to baseline (contralateral limb)
- Range of motion compared to baseline (contralateral limb)
- Patient reported outcome measures (SF-36, DASH, VAS Pain Scores)
- Maintenance of reduction compared to baseline (surgery)
- Fracture union assessment at the 6-,12-week follow-ups

2.4 Tertiary Endpoints

- Clinical CT to confirm healing, measure calcification, and record bone mineral density
- Clinical assessment of the fractured limb

3. STUDY DESIGN

3.1 Overview

The proposed study design is prospective, multi-center, single-arm, and non-randomized. RevBio is working to establish up to four (4) clinical sites. RevBio will perform site initiation visits to provide training to the investigator and its staff. Training will include information about study-specific procedures, a detailed review of the study protocol, instruction in completion of the electronic case report forms (eCRFs), informing the site about device instructions for use, and discussion of the regulatory requirements of the investigator. Patients will be recruited from the general patient population based on inclusion/exclusion criteria. Once they sign the informed consent form and complete the screening process they will be enrolled in the study and scheduled for surgery. All data will be reported to the FDA to evidence safety and efficacy and substantiate advancing to future stages in a larger expanded study.

3.2 Sample Size Calculation

Because this is a pilot study to demonstrate the safety and efficacy of use in patients, 20 patients will be enrolled to provide meaningful data for establishing outcome measures for assessment in a larger study population.

4. MATERIALS AND METHODS

4.1 Device Description

TN-MFF is a self-setting, mineral-organic, synthetic material. The clinical device consists of a sterile kit that includes 2 sealed mixing bowls containing TN-MFF powder, 2 pre-filled aqueous syringes, 2 mixing spatulas, 2 delivery syringes, and 2 delivery syringe cannulas, nested within a blister tray. This inner blister tray is housed within an outer blister tray, which is sealed to provide a sterile barrier. The system is designed to deliver two 5cc doses (10cc total in kit) of TN-MFF for use in open reduction internal fixation of fractures as an adjunct to hardware. Upon mixing, the adhesive is injected as a tacky viscous cement

to the surgical site before or after hardware placement. Its ionic bond strength to bone provides stability of bone fragments throughout the healing process.

4.2 Intended Use

Tetranite Bone Adhesive is intended to enhance fixation stability and promote bone healing in cases requiring additional structural support during the surgical repair of complex fractures. It provides intra-operative fixation and has the ability to adhere to and hold bone fragments in position throughout the healing process. It can also be used to fill gaps in bone as an osteoconductive scaffold.

4.3 Indication for Use

Tetranite Bone Adhesive for Extremity Fracture Fixation is indicated for open reduction procedures as an adjunct to internal hardware fixation in the treatment of unstable, complete articular fractures of the distal radius .

4.4 Instructions for Use, Handling, and Labeling

RevBio will provide the study Research Center with the required supply of product for the study. The product delivered for the study is to be used only for the subjects enrolled in the study and according to the clinical investigation plan. The study product will be used as described in the Tetranite IFU – Document #50030-01 and Operative Technique Guide Document #50043-01. The amount of Tetranite that is implanted in any given patient is up to the discretion of the surgeon, but it should not exceed 20cc of product (2 kits, 4 doses) . Tetranite for Extremity Fracture Fixation (TN-MFF) is a device designed and intended to provide immediate stabilization to distal radius fractures treated surgically by open reduction rigid fixation procedures. All device deficiencies shall be reported by the investigator to RevBio.

4.5 Patient Sample

For this protocol, there are intra-operative inclusion criteria that we cannot anticipate prior to surgery. Therefore, to yield a meaningful final study number, patient enrollment will continue until 20 patients have signed the Informed Consent and met the intra-operative inclusion criteria.

Enrollment will be prospectively stratified by age (Stratum A: <65 years; Stratum B: ≥65 years), with an intended 1:1 distribution, while permitting 8–12 patients per stratum.

4.6 Study Population:

Subjects must be greater than 21 years of age or older who require surgical intervention for a distal radius (AO/OTA Type 2R3C) fracture and who meet all the Inclusion/Exclusion criteria listed below.

4.7 Patient Identification

All enrolled patients will receive a unique study identification consisting of a study number (24003), a patient number associated with a treatment location, and a case number (a sequential number beginning with #1). For example, in patient number 24003-1-4, 24003 is the study number, 1 is the number of treatment location and 4 is the fourth patient enrolled for the location.

4.8 Randomization

This is a single-arm study and is not randomized.

4.9 Study Materials and Components

4.9.1. Storage

The study product will be stored in its original container until used and its access shall be controlled. Device Accountability

The Investigator must maintain an accurate and up-to-date accountability record of all study products received, used, discarded (opened, but non-used) and returned during the course of the study. This information shall be recorded in the Device Accountability Record Log. At each monitoring visit, the monitor will check the investigational device's accountability for accuracy and completeness. At the end of the study, the monitor or RevBio's delegate conducting the closeout visit will perform a final reconciliation of the device accountability (cross check between the Device Record Accountability Log, the shipments delivery notes and the acknowledgement of device receipts).

4.9.2. Return of Study Device

After treatment of the last subject, any remaining unopened study product at the study site must be returned to RevBio and acknowledged for receipt. A copy of the acknowledgement of the receipt must be filed in the Investigator File.

4.10 Risk Analysis, Risk/ Benefits

The device risk analysis and risk assessment for the TN-MFF device was conducted according to EN ISO 14971. Full results are included in the Risk Management Hazards Analysis (RevBio document 91164) and includes a list of anticipated adverse device effects (ADE) following the use of TN-MFF for distal radius fractures. Risks associated with the TN-MFF device and the procedures involved in its use are listed in the Instructions for Use Document #50030-01 and Operative Technique Guide Document #50043-01 as well as the Warnings/Precautions.

4.10.1. Warnings and Precautions

TN-MFF warnings and precautions are listed in the Instructions for Use Document #50030-01 and Operative Technique Guide Document #50043-01.

5. STUDY PROCEDURE SCHEDULE

5.1 Schedule of Procedures and Assessments

The schedule of administrative, treatment and evaluation visits will follow the matrix detailed in **Table 1**. The timing of the scheduled events listed in the table will be acceptable if it is within the tolerances listed. A record of procedure and evaluation dates will be maintained.

Table 1: Schedule of Procedures and Assessments

Visit #	Visit Name	Visit Window
Visit 1	Screening Visit	
Visit 2	Surgery	≤ 2 weeks from injury
Visit 3	2-Week Post-Operative Evaluation	2 weeks (+7/- 3) days from surgery
Visit 4	6-Week Post-Operative Evaluation	6 weeks (± 7) days from surgery
Visit 5	12-Week Post-Operative Evaluation	12 weeks (± 14) days from surgery
Visit 6	26-Week Post Operative Evaluation	26 weeks (± 30) days from surgery
Visit 7	52-Week Post Operative Evaluation	52 weeks (± 60) days from surgery

6. STUDY PROCEDURE DESCRIPTION

6.1 Signed Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations) to obtain informed consent in writing from each subject participating in this study prior to any

study related procedures. As part of the informed consent discussion with a potential subject, the investigator must provide an adequate explanation of the overall requirements/procedures of the study, purpose of the study, the nature of the planned treatment, any alternative procedures, and possible risks, complications, or benefits of the study. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from the study at any time for any reason without prejudice.

The informed consent must be approved by the appropriate IRB before consenting can begin. The informed consent form must be available in the primary language of the subject. It is written in accordance with the "Declaration of Helsinki" (as adopted by the 18th World Medical Assembly, 1964, and as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008), and Fortaleza (2013) (Appendix 2)) and applicable local regulations.

The appropriate IRB-approved consent form must be personally signed and dated by the subject and the person obtaining consent with a witness present for the signature. Investigators should keep the original signed informed consent document in a secure location. A copy of the signed consent form should be given to the subject. The Case Report Forms (CRFs) for this study contain a section for documenting informed consent, and this must be completed appropriately.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All consented and enrolled subjects should be informed of the new information, given a copy of the revised form and need to give their consent to continue in the study, unless the subject signed consent and was considered a screen failure.

6.2 Demographics

Demographics will be gathered after informed consent. Demographics will include gender, date of birth (age), ethnicity and race.

6.3 Inclusion/Exclusion Determination

An initial documentation evaluation will be conducted to determine whether the subject meets the Screening Inclusion/Exclusion criteria.

The study subject's documents may include the following:

- Screening Inclusion/Exclusion criteria determination
- Review of Medical history
- Pregnancy test (if required)
- Radiograph Imaging
- CT Imaging (Optional)

6.3.1. Study Inclusion Criteria

- Unilateral, unstable and/or displaced **distal radius** (AO/OTA type 2R3C) fracture.
- Standard treatment would consist of open reduction internal fixation (ORIF) with plate(s) and screws within 2 weeks of injury.
- Subject has no radiographic evidence of healing prior to surgery.
- Male or female, greater than 21 years of age
- Subject living independently and ambulatory at the time of injury.
- Subject, and/or subject's representatives are able and willing to provide informed consent and HIPAA authorization.
- Subject able and willing to meet all study requirements, including attending all post-index

6.3.2. Intra-Operative Inclusion Criteria

- No sign of active infection at the planned surgical site.
- Surgeons will decide whether or not the fracture site is a good candidate for TN-MFF use once the site is open to assess the bone and surrounding soft tissue for exclusionary criteria not apparent during pre-operative screening (e.g. vascular, nerve, ligamentous injuries or infection).

6.3.3. Study Exclusion Criteria

- Significant ligamentous disruption requiring independent repair
- Other fractures of the carpal bones or injured limb (Note: an associated ulnar styloid fracture is not exclusionary)
- Pathological fracture related to an underlying malignancy
- Open fractures
- A previous fracture in the injured bone within the last 12 months
- Presence of previous periprosthetic fracture or other orthopaedic implant in the injured bone
- Patients with presumptive diagnosis of named nerve or blood vessel injury
- Current infection (either superficial or deep) at the planned operative site
- Sepsis within one week from the planned index procedure
- History of radiotherapy to the area
- Active chemotherapy treatment
- Patients receiving treatment with biologics for systemic inflammatory disease (e.g., Enbrel)
- Physically or mentally compromised and unable to provide consent or perform functional examinations
- Subject has a condition with anticipated survival shorter than 12 months

6.4 Review of Medical History

The Charlton comorbidity index (CCI) will be used to evaluate patient medical history. This index contains 19 issues including diabetes with diabetic complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, metastatic tumor, and acquired immunodeficiency syndrome (AIDS), each of which was weighted according to their potential influence on mortality.

6.5 Pregnancy

A woman who is pregnant or planning to become pregnant at any point during the study duration cannot be enrolled in this study and will be considered a screening failure.

If a woman becomes pregnant during the study, a protocol deviation form should be completed. The subject should be followed for the duration of the pregnancy, without the study required CT imaging until term, and the outcome of the pregnancy should be documented.

6.6 Fracture Union

Fracture healing will be assessed by assigning a score of “expected healing progressing”, "union", “delayed union”, "nonunion" or "secondary intervention". Residual contrast agent from TN-MFF is expected to cause radiographic artifact on radiographs through the one-year post-op follow-up timepoint. In the event of a non-healed site, i.e., delayed union or non-union, a radiolucent margin or zone would still be present despite the residual contrast agent and therefore should not impede the determination of bone bridging or callus formation. In some cases, high-resolution CT scans may be required to detect evidence of bone bridging in events where the metal implant is blocking the view of one or more cortices or visualization of the bone micro-architecture will aid in the determination of the fracture union score.

Investigators will be provided with the following definitions:

- **Expected Healing Progressing** –fracture healing is progressing as expected (callus formation and/or cortical bridging is evident) within clinically relevant timeframe.
- **Delayed union** - insufficient fracture healing when callus formation has not been achieved within clinically relevant timeframe.
- **Union** - callus formation, cortical bridging, and/or disappearance of the fracture lines (no radiolucency) were visible on 3 of the 4 bone aspects (anterior, posterior, medial, and lateral). The first visit at which these criteria are met is considered the time of union radiographically.
- **Secondary intervention for delayed union** - any intervention, surgical or nonsurgical, that was performed to induce or accelerate fracture union. Examples included use of autograft, allograft or bone graft substitutes; IM nail dynamization; exchange nailing; or noninvasive modalities, e.g., ultrasound, magnetic field, or electrical stimulation.
- **Nonunion** - considered to be established when a minimum of 9 months have elapsed since injury and the fracture site showed no visibly progressive signs of healing for a minimum of 3 months (no change of fracture callus).

The definitions above for union, delayed union, secondary intervention for delayed union, and nonunion scores were used in a clinical study for fracture union assessment of INFUSE Bone Graft in the treatment of tibial shaft fractures were the product is intended to be resorbed and replaced with new bone during the healing process similar to TN-MFF.[6]

Radiographs will be digitized and evaluated by the investigator and a radiology panel. Review of each radiograph will be completed by all three members of the panel. An agreement of 2 of the 3 reviewers is necessary for all radiographic outcomes. If fracture union cannot be determined from digitized X-Ray images due to positioning, metal artifact, etc., the CT scan at the 26-week timepoint will be used to determine fracture union.

6.7 Imaging: Radiograph and CT

6.7.1. X-Ray

Posteroanterior, lateral, and oblique X-rays will be taken at all pre-operative and post-operative time points. Calibrated, radiopaque rulers will be placed in the same plane as the area of interest for image scaling and to obtain anatomical measurements at all timepoints.

6.7.2. CT Specific Parameters

CT scanning will be performed on commercial CT scanners using the standard departmental protocol and using the settings stated below. No intravenous contrast will be given. Multidetector CT images are obtained with a maximum slice thickness and pixel spacing of 0.625 mm with 120 kV photon energy and a reference mAS of 360 for systems with iterative software, and 450 mAs without iterative software. The Z-axis coverage extends from the distal end at the wrist joint, encompassing the distal articular surfaces of the radius and ulna, and extends proximally to cover at least 150 mm from the distal end of the radius. Images are reconstructed in multiple planes for evaluation.

When possible, an HR pQCT scanner should be used at a standard resolution of 61 µm with a region of interest of 100 mm at the distal end of the radius, encompassing the fracture site.

6.8 Assessment of Adverse Events

Following surgery and at each visit until the end of the study, the Investigator will determine if any adverse events occurred since the last study visit by speaking with the subject and reviewing any medical records. These Adverse Events (AEs), along with any adverse events from the current study visit, should be documented and reported as described in **Section 9.29** of the protocol. In addition, the Investigator will evaluate the status of any ongoing adverse events throughout the study as specified in **Section 9.4.9.4**

6.9 Surgical Steps Using TN

After site preparation and initial evaluation of the fracture, surgeons will decide whether to use TN-MFF as an intra-operative adhesive to help reduce fragments prior to hardware placement or to use TN-MFF to fill gaps in bone post-reduction and hardware fixation.

TN-MFF will be activated by injecting liquid from pre-filled syringe into bowl, then loaded into the delivery syringe using the spatula, and injected into the site. No more than 20cc will be implanted. Standard techniques for hardware fixation will be followed. The overlying soft tissue will be closed in a standard, sterile layered fashion.

6.10 Patient Reported Outcome Measurements

Patient reported outcomes will be measured using the following:

- **DASH screening**
  The Disabilities of the Arm, Shoulder, and Hand (DASH) screening uses 30 core questions scored on a 5-point scale, covering daily activities, pain, and social participation, with results scaled from 0 (no disability) to 100 (severe disability). DASH is a key measure of treatment efficacy in restoring upper limb function.
- **SF-36 assessment**
  The SF-36 (Short Form Health Survey) generates scores for eight domains (physical functioning, pain, mental health, and social functioning) and a composite physical and mental health score, scaled from 0 (poor health) to 100 (excellent health). The SF-36 is widely used to evaluate treatment impact on quality of life.
- **VAS assessment**
  The Visual Analog Scale (VAS measure subjective experiences such as pain intensity. Patients mark their level of discomfort on a 10 cm line, with endpoints labeled "no pain" (0) and "worst pain imaginable" (10). The VAS provides a quick, quantitative assessment of treatment impact on pain levels.

6.11 Patient Functional Outcome Measures

The following patient functional outcomes will be measured and compared to the contralateral untreated limb:

- **Grip strength**
  Grip strength will be measured by hand dynamometer apparatus. Three assessments will be obtained for the treated and the uninjured hand at each interval. The average of the treated side will then be expressed as a value of the uninjured hand.
- **Range of motion**
  Range of motion will be assessed using wrist extension, flexion, ulnar deviation, radial deviation, pronation, and supination measurements. Summary statistics for range of motion will be presented at each follow-up visit.

6.12 Clinical Assessment of Fractured Limb

Clinical assessment of the fractured limb will be addressed using the following attributes:

- Wound
- Pain
- Swelling
- Tenderness
- Neurovascular status

- Infection
- Weight-bearing status

6.13 Post-Operative Protocol

The post-operative procedure will be up to the discretion of the surgeon to prescribe immobilization, pain and swelling control, range of motion, and wound care protocols.

7. CLINICAL IMAGING ANALYSIS

7.1 Radiographic Analysis

Anterior-posterior and lateral X-rays will be taken at all pre-operative and post-operative time points. If the standard views do not provide sufficient visualization of the fracture, oblique radiographs may be utilized. Radiographic assessments conducted at all time points will ensure there is no device fracture, migration, malalignment, or loss of reduction or fixation.

Additionally, radiographs will be assessed immediately following surgery and at each post-operative follow-up timepoint to measure Palmar inclination (PI), ulnar variance (UV), and radial inclination (RI). Palmar Inclination is the angle between a perpendicular to the longitudinal axis of the radius and the line between the dorsal and volar margins of the joint, indicating the angulation of the articular surface. A positive value corresponds to palmar inclination, while a negative value indicates dorsal inclination. Ulnar Variance measures the relative length of the ulna to the radius, defined as the distance (in mm) between two lines perpendicular to the radial axis: one at the ulnar joint surface and the other at the sigmoid notch, a prominent ulna is indicated with a positive value. Radial Inclination is the angle between the radial joint surface line (a line between the styloid process of the radius and the ulnar corner of the lunate fossa) and a perpendicular to the longitudinal axis of the radius[7].

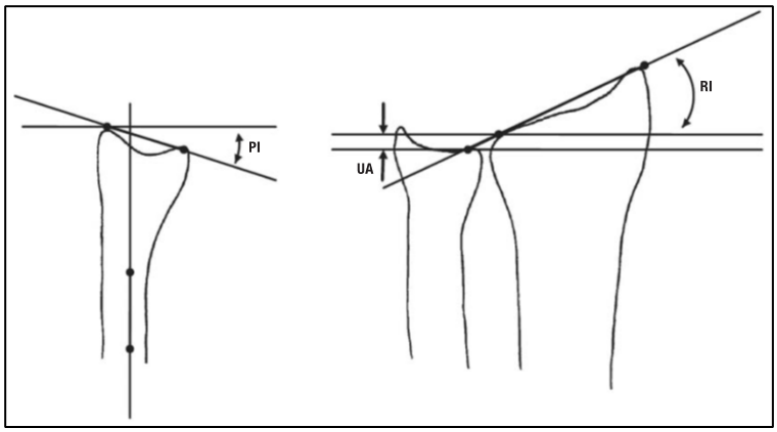

Figure 1. Palmar Inclination (PI), Ulnar Variance (UV) and Radial Inclination (RI) measurements to assess maintenance of reduction[1]

Radiographs will be digitized and evaluated by the investigator and a radiology panel. Review of each radiograph will be completed by all three members of the panel. An agreement of 2 of the 3 reviewers is necessary for all primary radiographic outcomes.

7.2 CT Analysis

CT scans will be assessed as a secondary analysis for measuring Palmar inclination (PI), ulnar variance (UV), and radial inclination to assess maintenance of reduction. Additionally, bone micro-architecture will be assessed, including trabecular and cortical bone parameters such as thickness, area, bone volume,

total volume, volume fraction, porosity and trabecular number and separation to evaluate substitution of TN-MFF with newly formed bone if possible based on the scanner resolution. These metrics also enable the assessment of bone quality, density, fracture union and structural integrity during bone healing in addition to the digitized x-rays.

8. PROTOCOL RELATED PROCEDURES

8.1 Early Withdrawal

Any subject may withdraw from the study at any time without prejudice and will be offered alternative treatment for his/her condition. Subjects will be advised of the need for the prescribed follow-up visits for their ongoing care, well-being, and collection of any safety data.

The Investigator may withdraw any subject from the study in the case of:

- Non-compliance with the protocol
  - Important Protocol Deviations (IPD)
  - Serious Breaches (SB)
- Failure to attend the follow-up visits
- Serious Adverse Event (SAE) or adverse event (AE), which in the opinion of the Investigator prevents the subject's further participation in the study.

The subject withdrawal will be documented on a study termination form and must include the reason for the subject's withdrawal. Efforts should be made to capture the primary study endpoint for each subject prior to withdrawal, if possible.

Subjects withdrawn from further study procedures and assessments will continue to be followed to ensure patient safety. Subjects withdrawn for IPDs and/or SBs will continue to be followed to ensure patient safety and their study data will be segregated from final study analyses.

8.2 End of Study

The study will be considered completed once all patients have completed the 52-week post-operative visit. This will be documented on a study completion form.

8.3 Subject Replacement Policy

Subjects withdrawn after enrollment may be replaced, at the discretion of the PI and Study Monitor, if the withdrawal or discontinuation is not due to a device- or procedure-related adverse event.

8.4 Protocol Deviations

Deviations from the procedures established in the protocol are discouraged. If a deviation occurs, the study center must record the deviation on the appropriate CRF. The sponsor shall be notified immediately of any deviations in informed consent or Inclusion/Exclusion criteria. Any deviation from the protocol (including deviations from the expected study visit windows) may jeopardize the study outcome. Non-compliance of the subjects, as well as of the Investigators, may lead to the closure of the respective study center.

Important Protocol Deviations (IPD), deviations which might affect data integrity or patient rights/safety, will lead to subject withdrawal from further study procedures. These subjects will continue to be followed to ensure patient safety and provide appropriate treatments. IPDs include, but are not limited to, protocol deviations such as:

- enrolling patients who fail to meet all inclusion/exclusion criteria,

- additional treatment procedures or techniques not foreseen in the study protocol,
- improper preparation of TN-MFF not conforming to IFU, and
- other significant deviations from the study protocol or product Instructions for Use.

Serious Breaches (SB), deviations which are likely to significantly affect data integrity or patient rights/safety, must be reported to the Sponsor within 2 days of their occurrence. SBs include, but are not limited to:

- instances where a subject is enrolled in study procedures while being pregnant
- presenting with or undergoing treatment(s) for cancer or other diseases which are likely to interfere with healing post-surgery, e.g., radiation therapy to treated limb; chemotherapy; anti-inflammatory treatment such as systemic corticosteroids, rituximab, etc.; or other medical conditions noted in exclusion criteria.
- sharing of patient's PHI outside of study personnel, and
- other significant deviations from the study protocol or product Instructions for Use which are likely to affect patient's rights/safety or data integrity.

9. EVALUATION OF ADVERSE EVENTS

For the avoidance of doubt, all AE/SAEs as defined below should be collected, fully investigated and documented in the source document and appropriate case report form for all subjects from the time of the signing of the informed consent until the last protocol-specific procedure. Documentation includes dates of event, treatment, outcome, assessment of seriousness and causal relationship to the device and/or study procedure (rational to be provided).

The severity of each AE will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE. A general guideline to CTCAE and the grading scale can be found here: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

9.1 Adverse Event Definitions:

9.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or surgical procedure. This definition includes events related to the investigational medical device or events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

9.1.2. Serious Adverse Event (SAE)

An adverse event will be considered serious if the event is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and receives a score of 4 or 5. For instance, it will include any adverse event that:

- led to a death
- led to a serious deterioration in the health of the subject, that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or

- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- led to fetal distress, fetal death, or a congenital abnormality or birth defect

NOTE: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered to be a serious adverse event.

9.1.3. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Any adverse event which the clinical investigator believes has even a possible relationship to the device will be classified as an ADE.

9.1.4. Serious Adverse Device Effect (SAE)

A SAE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

9.1.5. Unanticipated Serious Adverse Device Effect (UADE)

An UADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

9.1.6. Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. A summary of the classification for adverse events is reported on the specific CRFs.

9.2 Assessment of Adverse Events

In the event of an adverse event, the investigator or another suitably qualified clinician who is trained in recording and reporting AEs and has been delegated to this role (such delegation must be captured in the study site delegation log) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event. Each adverse event should be assessed for seriousness according to the CTCAE v5.0 scale, relationship to the study device or the procedure, severity, outcome, and expectedness, as described below, by the Investigator.

9.2.1. Seriousness

An adverse event will be described as serious if it meets the criteria outlined in the CTCAE v5.0. The rationale for the assessment shall be provided in a short narrative.

9.2.2. Relationship to the Study Device

The investigator should assess the relationship of the adverse event to the product (TN-MFF device) and provide the rationale in a short narrative. The relationship should be assessed using the following categories:

- Definitely related – There is a reasonable causal and temporal relationship between the treatment with the study device and the adverse event.
- Probably related – There is a reasonable causal and temporal relationship between the treatment with the study device and the adverse event, but a potential alternative cause may be present.
- Possibly related – The causal and temporal relationship between the treatment with the study device and the adverse event is less likely; however, the determination that there is no relationship cannot be made.

- Not related – A causal relationship with device application can be definitely excluded. By definition, all AEs/ADEs, with a start date before the surgery procedure at Visit 2 must be assigned a “not related” relationship with study device.

NOTE: Device deficiencies that might have led to an SAE are always related to the medical device.

9.2.3. Relationship to the Procedure

The investigator should assess the relationship of the adverse event to the placement of TN-MFF device and provide the rationale in a short narrative. The relationship should be assessed using the categories described herein.

9.2.4. Severity

Each adverse event should be assessed by the investigator for its severity, or the intensity of an event experienced by a subject, using the CTCAE v5.0.

The maximum severity observed is to be recorded, except if there is a significant worsening in an AE/ADE severity after device intake, then the change will be tracked as a new AE/ADE record as follows:

- The same wording describing the original AE/ADE must be used.
- Outcome of the initial entry should be designated as 'worsened'.
- The end date of the previous AE/ADE must equal the start date of the new AE/ADE.

9.2.5. Outcome

The outcome should reflect the status of the adverse event at the time of recording.

- Resolved - The subject fully recovered from the event without any sequelae. This option also applies when it is unknown whether there are sequelae.
- Resolved with sequelae - The subject’s condition stabilized despite the persistence of sequelae (e.g., lesion or medical condition which is a consequence of the event). This option does not apply to irreversible congenital anomalies (see under “ongoing”).
- Ongoing - The subject has not yet recovered from the event. By convention, in the case of an irreversible congenital anomaly, the “Ongoing” option should be chosen and understood as “Not recovered/Not resolved “. The same applies to conditions that are not yet resolved, but are controlled by medication (e.g., diabetes, epilepsy) and therefore may not have any symptoms.
- Worsened - The severity of the AE/ADE increased.
- Fatal - The event is related to a death; whether it caused death or contributed to it. If the subject died of a different cause, prior to resolution of the AE/ADE, the outcome of this AE/ADE should be designated “Ongoing”, and not “Fatal”, and an end date should not be specified.
- Unknown - Knowledge of the current status of the AE/ADE is truly not available to the investigator (i.e., event was ongoing at last observation, but no further contact with the subject could be established). However, all efforts should be made to determine the outcome of any AE, especially that of an SAE/SADE.

9.2.6. Expectedness

If the adverse event is judged to be related to the device, the investigator will assess expectedness based on knowledge of the reaction and any relevant product information as documented in the IFU and current protocol. The event will be classed as either.

- Expected - the reaction is consistent with the effects of the device listed in the IFU and protocol.
- Unexpected - the reaction is not consistent with the effects listed in the IFU and protocol.

The Risk Management Hazards Analysis (91164) presents the potential anticipated adverse device effects following the placement of TN-MFF for the extremity fracture fixation.

9.3 Procedure for Reporting Adverse Events

Adverse event reporting will begin at the time a subject provides written informed consent and ends after a subject withdraws from the study or completes the final study visit. For screen failure subjects, any AEs, ADEs, and DDs that occur from the time of informed consent up until the date on which the subject is deemed ineligible for the study will be recorded on a case report form. Only one AE/SAE case report form should be completed per event. To ensure patient confidentiality, the following reports will include the patient number only.

9.3.1. AE Reporting

In the occurrence of an AE, data should be entered into the AE case report form in the EDC system within five working days of awareness of the event. Safety reporting to the IRB should occur according to the requirements of the local IRB.

9.3.2. SAE Reporting

In the occurrence of a serious adverse event (SAE), expedited reporting requirements are followed. The SAE case report form should be completed in the EDC within 24 hours of awareness of the event. RevBio will receive an automated notification generated by the EDC system. Safety reporting to the appropriate IRB should occur according to the requirements of the local IRB. It is recognized that in some cases SAEs will be treated by someone other than the investigator and the investigator may not have immediate knowledge of the event. The investigator should report an SAE as soon as he/she has knowledge of the event within the above time frame irrespective of when the actual event occurred.

9.3.3. DD Reporting

The Investigator should report all device deficiencies to RevBio by submitting a description to the following email address: reg_complaints@revbio.com

If appropriate, the product shall be returned in appropriate packaging by courier (trackable method) directly to:

Attn: Regulatory Affairs
RevBio
600 Suffolk Street, Suite 250
Lowell, MA 01854

When a device deficiency leads to a potential AE, the AE case report form in the database needs to be completed in a timely manner. Moreover, device deficiencies with SADE potential must be recorded in the SAE case report form and follow the expedited reporting requirements (within 24 hours).

9.3.4. ADE Reporting

Adverse device effects must be recorded and submitted to RevBio by completing the AE case report form in the EDC system within five working days of awareness of the event. Safety reporting to the local IRB should occur according to the requirements of the appropriate.

9.3.5. SADE Reporting

In the occurrence of a serious adverse device effect, expedited reporting requirements are followed. The SAE case report form should be completed within 24 hours of awareness of the event in the EDC system. RevBio will receive an automated notification generated by the EDC system.

The product safety officer at RevBio will work with the Investigator to determine whether the event is anticipated (ASADE) or unanticipated (USADE). In case of an USADE, the investigator must promptly notify its reviewing appropriate IRB as soon as possible, but no later than ten (10) working days after first learning of the event.

9.3.6. Additional Safety Reporting

RevBio will report additional safety information to the center that is relevant to the protocol or study device and may affect the risk/benefit ratio, the rights, safety or welfare of subjects, or the integrity of the study. Such reports may include notification of any changes to the instructions for use, any publications or interim reports, or any product recalls.

9.4 Monitoring of Subjects with Adverse Events

Any AE that occurs during this study must be monitored and followed-up by the investigator until one or more of the following have occurred:

- The AE is resolved,
- Pathological laboratory findings have returned to normal,
- Steady state has been achieved, or
- It has been shown to be unrelated to the study products.

The outcome of an event will be pursued until resolution or until the last data queries are issued following the subject's last study visit. For screen failure subjects, ongoing AEs, ADEs, and DDs must be followed and updated until the date the subject is deemed a screen failure. For subjects documented as lost to follow-up, ongoing AEs, ADEs, and DDs will not be followed. It is the responsibility of the sponsor to cooperate with the investigator to assure that any necessary additional therapeutic measures and follow-up procedures are performed.

9.5 Stopping Criteria

Enrollment in the study will be temporarily halted, and reviewed by the CEC prior to resuming enrollment, if any of the following conditions are met and the events are probably or definitely related to the study device:

- Patient Death
- Overall UADE rate (if greater than 20%)
- Necrosis related adverse events that require surgical intervention (if greater than 20%)

10. EVALUATION CRITERIA

10.1 Analysis of Primary Endpoint

The primary analysis will consist of the following:

- Demonstrate that TN-MFF can be safely used in patients as evidenced by the rate of serious device related adverse events from the time of fixation to 26 weeks post-procedure.
- DASH scores decrease, in at least 85% of patients when compared to baseline (screening), at 26 weeks.
- Fracture union success in at least 85% of patients at 26 weeks.

10.2 Analysis of Secondary Endpoints

The secondary analysis will consist of the following:

- Grip strength has recovered to at least 50% when compared to contralateral limb
- Range of motion has recovered to at least 50% when compared to contralateral limb
- VAS Pain Scores decrease when compared to baseline (screening)
- Patient reported outcome measures (SF-36) improve when compared to baseline (screening)
- DASH scores decrease when compared to baseline (screening)

- Maintenance of reduction (radial inclination, palmar inclination and ulnar advancement) shows no significant change ($p > 0.05$) compared to baseline (post-op)
- Radiographic assessment of fracture healing/union at 6- and 12-weeks

10.3 Analysis of Tertiary Endpoints

All tertiary endpoints will be summarized descriptively. CT/radiographic data for tertiary endpoints will be sent for central review.

10.4 General Statistical Methods

As this is a Pilot trial only descriptive statistics will be used, including mean, standard deviation, and range.

11. Primary and secondary endpoints will be summarized overall and by stratum using descriptive statistics. Given the sample size, no formal hypothesis testing between strata is planned; however, we plan to perform exploratory subgroup analysis.PROTOCOL DEVIATIONS AND VIOLATIONS

Occasionally during the study, deviations from the procedures established in the protocol may occur. Any anticipated deviation from the protocol is reason to contact the clinical research department at RevBio. The deviation will be documented on the appropriate data form and handled appropriately.

12. STUDY MANAGEMENT

12.1 Regulatory and Ethical Requirements

12.1.1. Informed Consent

Informed consent will be obtained from all subjects prior to study participation as described in **Section 6**.

12.1.2. Institutional Review Board (IRB)

Prior to initiation of any study procedures, the protocol and informed consent will be submitted to the appropriate IRB for review and approval. In addition, any amendments to the protocol or informed consent will be reviewed and approved (if necessary) by the IRB. The sponsor must receive a letter documenting the IRB approval at the center prior to the initiation of the study at the center.

The investigator is responsible for providing the appropriate reports to the IRB during the course of the clinical study. This will include the following:

- Informing the IRB of the study progress periodically as required.
- Reporting any unanticipated serious adverse device effects within 10 working days of becoming aware of the event
- Reporting any deviations from the protocol that adversely affect the risk/benefit ratio, the rights, safety, or welfare of the participants, or integrity of the study
- Providing any other reports requested by the IRB

12.2 Reports and Record Management

12.2.1. Case Report Forms

Digital Case Report Forms (CRFs) will be prepared by RevBio for the registration of data. These forms will be used for the entire duration of the study. The completed CRFs will continuously be collected by

the study monitor for analysis and storage. Investigators will keep a copy of the CRFs and will maintain these records for at least three years.

CRFs are required for all individuals enrolled in the study. Errors should be lined out. Initial and date the correction with notation of the reason for the change. CRFs will be considered complete when all data queries have been fully addressed.

The investigator will be responsible for the accuracy of the data entered on the Electronic Case Report Forms (eCRFs). The investigator will also allow a RevBio representative and/or regulatory bodies to review the data reported on the case report form with the source documents as far as is permitted by local regulations.

12.2.2. Source Documents

Source documents are defined as the original point of entry of a specific data point. Source documents will include, but are not limited to, progress notes, electronic data, computer printouts, imaging, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the investigator and made available for inspection by authorized persons.

12.2.3. Records/Data Retention

Original imaging, photographs, and study documents will be maintained at the research center in a file established for this study. All study documentation needs to be stored at the research center for at least fifteen (15) years following the completion of the study, as specified by the sponsor. The investigator should have access to the study documents in order to answer any queries associated with the study. All other study records will be kept by RevBio once the study has been completed. These records will be maintained at RevBio according to RevBio's standard operating procedures.

12.3Monitoring

A Study Monitor from RevBio will be assigned to monitor the study. Before the start of the study, the monitor will contact the principal investigator to ensure that the protocol and study logistics are well-understood. Specific instructions as to the proper completion of the clinical data forms will be provided. At various time points in the study, a review of patient records may be needed to ensure accuracy of data. In this case, study patient charts must be made available to the study monitors during site visits.

12.3.1. Study Initiation Visit

The monitor will schedule a site initiation visit in order to make sure all study documents are in place and that all the site personnel that will participate in the study are trained in the study procedures. The monitor will ensure during the study initiation that the investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study.

12.3.2. Routine Monitoring Visits

Monitoring visits will be scheduled and conducted periodically, but at a minimum annually to review the following:

- The study is in compliance with the currently approved protocol/ amendment(s); deviations will be discussed with the responsible investigator, documented, and reported to the sponsor and, if required, reported to the IRB
- The study is in compliance with Good Clinical Practice (GCP) and with the applicable regulatory requirements.
- Only authorized investigators/ clinical personnel are participating in the clinical investigation.
- Device accountability including adequate supply at center, proper storage, and documentation of device traceability.

- The reported study data entered on CRFs are accurate, complete, and verifiable from source documents
- All adverse events and serious adverse events are reported correctly. In cases where there is missing information about an adverse event or missing evidence to support the investigator's assessment, a monitor will review and discuss the adverse event with the responsible investigator.
- The reason for a subject's withdrawal has been documented
- The investigator will allow RevBio to have access to all study documents during each monitoring visit for a thorough review of the study's progress.

12.3.3. Study Closeout Visit

After the last subject has completed the study and the database has been cleaned, the closeout visit will be conducted at the center. Study Termination

At study termination, a Clinical Investigation Report will be prepared by the sponsor, even if the study was terminated prematurely.

The study can be terminated early at the discretion of the investigator or the sponsor in the case of any of the following:

- Occurrence of adverse device effects unknown at the start of the study with respect to their nature, severity, and duration, or the unexpected excessive incidence of known adverse device effects.
- New scientific knowledge obtained after the start of the study showing the ethical claim of the study is no longer valid

12.3.4. Center Discontinuation

The study Center will be closed, and the study terminated under the following circumstances:

- The Center is not recruiting a sufficient number of subjects or is unlikely to recruit a sufficient number of subjects.
- The Center does not respond to study management requests.
- Repeated protocol violations have been discovered that affect the integrity of the study or the study data

12.4Protocol Amendments

Any proposed change to the protocol is to be discussed with the clinical monitor in a timely manner. Once both the investigator and the sponsor have accepted the changes, a written addendum to the protocol or a revised protocol will be sent to the investigator for signature and then submitted for approval to the IRB. Copies of addenda and revised protocols will be kept by both parties in their respective files.

12.5Publications

Analysis of data will be conducted by RevBio and the final report will be prepared by RevBio with input from the investigators. Any publications or presentations utilizing the data from this study must be reviewed by RevBio prior to submission according to the time frame specified in the clinical study agreement.

EXAMPLE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol: DVAL24003-P

Title: A Pilot Clinical Study to Evidence Safety and Efficacy of Fracture Fixation of the Distal Radius using a Bioresorbable Bone Adhesive to Augment Metal Hardware

Version: 3.0

I have read the foregoing protocol and agree to conduct the study as outlined. I agree that the examinations and follow-up visits required by the study protocol are in accordance with the standard treatment plan for distal radius fractures.

Signature:

Principal Investigator	Date

Received by Sponsor:

Brian Hess, Study Director	Signature of Study Director	Date

13. REFERENCES

[1]Watts, Nelson B., et al. "National Osteoporosis Foundation 2008 Clinician's Guide to Prevention and Treatment of Osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): what they mean to the bone densitometrist and bone technologist." *Journal of clinical densitometry: the official journal of the International Society for Clinical Densitometry* 11.4 (2008): 473-477.

[2]Burge, Russel, et al. "Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025." *Journal of bone and mineral research* 22.3 (2007): 465-475.

[3]Azad, Ali, et al. "Epidemiological and treatment trends of distal radius fractures across multiple age groups." Journal of wrist surgery 8.04 (2019): 305-311.

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[5] Bartl, Christoph, Dirk Stengel, Florian Gebhard, Thomas Bruckner, and Study Group ORCHID. "The treatment of displaced Intra-articular distal radius fractures in elderly patients: a Randomized Multi-center Study (ORCHID) of open reduction and volar locking plate fixation versus closed reduction and cast immobilization." Deutsches Ärzteblatt International 111, no. 46 (2014): 779.

[6]PMA P000054 for INFUSE Bone Graft approved April 30, 2004