Title: Clinical and Radiographic Outcomes Using ViviGen® Cellular Bone Matrix for Complex Hindfoot Arthrodesis

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PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

INSTRUCTIONS

- This should include a referenced systematic evidenced-based review when possible.
- If this study involves qualitative research explain the major constructs of your study.
- Do not state in this section what you plan to do in this study. This information should be entered later under "What will be done in this protocol?"
- Do not include the bibliography in this section.
- For studies submitted under the Expedited review criteria, this section need not be more than a few paragraphs.
- For those studies where data will be analyzed collaboratively by multiple sites doing a similar study for which there is no common protocol (Collaborative Site Analysis Study) include a description of the common scientific goals/ procedures/data points.
- If this is a FIVE YEAR UPDATE make sure the information throughout the protocol includes the most current information.

Answer/Response: Arthrodesis procedures for the ankle and hindfoot are performed to correct deformity and treat end-stage arthritis. However, recent literature has demonstrated that 10-40% of ankle fusions result in non-union (1,2). For triple arthrodesis (talonavicular, subtalar, and calcaneocuboid joints), published rates of non-union range from 0-10% (3). However, recent literature from our institution demonstrated significantly higher rates of non-union when calcaneo-cuboid sparing hindfoot arthrodesis was performed (4). Given that not every non-union results in a revision surgery, it is likely that the published rates of non-union underestimate the true rate of this complication. Due to the extended period of convalescence after these major arthrodesis procedures, non-union is a devastating outcome. Loss of mobility, loss of income from employment, and increased health care expense and patient risk for a second procedure contribute to the economic and emotional impact of non-union upon these patients.

Currently, many alternatives to autograft harvest are being evaluated for foot and ankle arthrodesis. Given the known complications of autograft harvest (incision pain, nerve injury, infection, 1), alternatives which possess osteogenic, osteoconductive, and osteoinductive properties are an attractive option when supplementing complex hindfoot arthrodesis procedures. A recent publication demonstrated a superior fusion rate for purified recombinant human platelet-derived growth factor BB homodimer (rhPDGF-BB) when compared to autograft (5). However, arthrodesis rates, as confirmed on CT scan, were only 84% and 65% respectively.

ViviGen (Depuy Synthes) is a cellular bone matrix, which includes viable osteoblasts within a corticocancellous and demineralized bone carrier, represents a unique alternative to autograft or existing products which utilize mesenchymal stem cells. ViviGen Cellular Bone Matrix is a Human Cells, Tissues, and Cellular and Tissue-based Product (HCT/P) as defined by the U.S.

Food and Drug Administration in 21 CFR 1271.3(d). ViviGen Cellular Bone Matrix is processed from donated human tissue, resulting from the generous gift of an individual or his/her family. This product is classified as a **biologic** by the FDA. Given our encouraging early data using Vivigen for complex and revision arthrodesis procedures in the foot and ankle, our Foot and Ankle Clinical research group at the University of Virginia wishes to conduct a prospective study to evaluate 1-Year implant survivorship in subjects who receive the implant when used for primary ankle or hindfoot arthrodesis procedures as part of their clinical care.

Our study would prospectively follow primary ankle or hindfoot arthrodesis procedures. Ankle arthrodesis, tibiotalocalcaneal arthrodesis, subtalar and triple arthrodesis procedures would be included in this cohort, and CT scan would be utilized to demonstrate successful arthrodesis (defined by >50% fusion). Patient outcome measures including Foot and Ankle Activity Measures, AOFAS hindfoot score, and VAS pain scores would be recorded pre-operatively and for 1 year post operatively.

The purpose of this study is to examine 1-year outcomes. ViviGen Cellular Bone Matrix is being given as part of clinical care. The only research procedures are questionnaires and blood draw for Vitamin D.

Objectives/Hypothesis

INSTRUCTIONS:
If this study involves biomedical research clearly state the objectives and hypotheses and clearly define the primary and any secondary outcome measures. If this study involves qualitative research clearly state your research hypothesis or question.

This section should not include information already included in other sections such as background information or information from the procedures section.

Answer/Response: To evaluate 1-Year implant survivorship in subjects who receive the implant when used for primary ankle or hindfoot arthrodesis procedures.

Study Design: Biomedical

1. Will controls be used?

Answer/Response: No.

►IF YES, explain the kind of controls to be used.

Answer/Response:

2. What is the study design?

Example: case series, case control study, cohort study, randomized control study, single-blind, double-blind, met-analysis, systematic reviews, other. You may also view the IRB-HSR Learning Shot on this topic to help you answer this question. (http://www.virginia.edu/vpr/irb/learningshots/Writing_protocol_June09/player.html

Answer/Response: This is a post-market, prospective, non-randomized, PI initiated, open-label clinical evaluation of the implant for use in primary ankle or hindfoot

arthrodesis. Data will be collected at specific time points and entered into case report forms (CRFs) based on the information contained in the patient medical records.

3. Does the study involve a placebo?

Answer/Response: No.

►IF YES, provide a justification for the use of a placebo

Answer/Response:

Human Participants

Ages: 18-80
Sex: All
Race: All

Subjects- see below

INSTRUCTIONS: For question 1-4 below insert an exact #. Ranges or OPEN is not allowed. This # should be the maximum # you expect to need to enroll (i.e. sign consent) If you are only collecting specimens the number of participants should equate to the # of specimens you need. If you are collecting only data from a chart review the number should designate the number of subjects whose medical records you plan to review. Age/ Sex/Race criteria should designate the demographics of participants from whom you will obtain the specimen/data.

1. Provide target # of subjects (at all sites) needed to complete protocol.

INSTRUCTIONS: If this is NOT a database protocol, this number should be the same as the number of subjects needed to obtain statistically significant results.

Answer/Response: 15

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

Answer/Response: 10%.

3. How many subjects will be enrolled at all sites?

INSTRUCTIONS: This number must be the same or higher than the # from question # 1 in order to account for the # of screen failures, dropouts, withdrawals described in question # 2.

Answer/Response: 18.

4. How many subjects will sign a consent form under this UVa protocol?

INSTRUCTIONS: If the protocol does not have a consent form- the number listed here should reflect such things as the number of subjects from whom specimens will be obtained, the number of charts to be reviewed etc.

Answer/Response: 18.

Inclusion/Exclusion Criteria

INSTRUCTIONS:

- The inclusion and exclusion criteria should be written in bullet format.
- *This item applicable if the study will require consent (verbal or written).* Unless there is a scientific reason for not recruiting a certain type of vulnerable population(e.g. not enrolling fetuses, neonates or children in a study regarding Alzheimer's) list the following vulnerable populations under either Inclusion or Exclusion criteria below: pregnant women, fetuses, neonates, children, prisoners, cognitively impaired, educational or economically disadvantage, non- English speaking subjects .
- If you will not enroll subjects who do not speak English because certain procedures cannot be carried out if the subject does not speak English (e.g. a survey is not validated in other languages) insert the following as an Inclusion Criteria: Willingness and ability to comply with scheduled visits and study procedures.
- If this is a collection of only retrospective* specimens or data, the inclusion criteria must include a start and stop date for when specimens/ data will be collected.
- The stop date must be prior to the version date of this protocol.
- *Retrospective: all specimens are in a lab at the time this protocol is approved by the IRB. All data exists in medical records or records from previous studies at the time this protocol is approved by the IRB.

1. List the criteria for inclusion

Answer/Response:

- Patient with prescribed standard of care unilateral hindfoot ankle arthrodesis procedure who will receive the ViviGen® Cellular Bone Matrix as part of their clinical care
- Age 18-80
- Willing to complete all follow up evaluations

2. List the criteria for exclusion

Answer/Response:

- Prior infection at site of planned arthrodesis
- Inability to maintain non-weight bearing status
- Bone defect requiring more than 10 cc of bone graft material
- A Vitamin D level of < 30ng/mL pre-operatively
  -Testing can be completed up to 1 week prior to surgery
- Inadequate bone stock to allow for rigid internal fixation.
- BMI greater than 40
- Pregnancy per review of current lab results in medical record of childbearing females.
- Cognitive inability to provide informed consent
- Tobacco or nicotine use 6-weeks prior to surgery
- Hemoglobin A1C >8.0
- Not-English speaking individuals

3. List any restrictions on use of other drugs or treatments.
Answer/Response: N/A.

Statistical Considerations

1. Is stratification/randomization involved?
Answer/Response: No.

►IF YES, describe the stratification/ randomization scheme.

INSTRUCTIONS:
The stratification factors and/or the randomization plan should be identified. If there is no randomization component or important patient characteristics that will be used in treatment allocation or data analysis, a statement to this effect should be included.

Stratification factors: These are pretreatment patient characteristics which could be balanced across treatment arms by design or may be used to determine starting dose or treatment allocation.

If randomization is going to be used, the details of the randomization plan should be described.

The description should include:
--the method and timing of randomization
--the type of randomization scheme that will be used in the study
--whether or not the randomization masked/blinded/if so, then to whom is it masked/blinded
--who has access to the randomization scheme

Answer/Response: NA

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
_____ Other: Specify Answer/Response:

2. What are the statistical considerations for the protocol?

The objectives section and the statistical section should correspond, and any objective for which analysis is unfeasible should be deleted. Also, the estimates and non-statistical assumptions of the statistical section should be supported by discussion in the background section.

The answer to this question should include:
--Study Design/Endpoints

--Recap of study objectives and endpoint definitions. An assessment of how study objectives will be assessed by identifying & defining which endpoints will be used to assess each component of the study objectives.
--The study design should include contingencies for early stopping, interim analyses, stratification factors (If applicable), and any characteristics to be incorporated in analyses.
--The power/precision of the study to address the major study endpoint(s), the assumptions involved in the determination of power/precision.
--If statistical hypothesis testing is included then specify the null and alternative hypotheses, the test statistic, and the type I and II error rates
--If precision of an estimate, then provide a definition for precision
--If other, then specify

Answer/Response: We will compare primary outcome measures as a binary outcome using chi-square or Fisher exact analyses using existing failure rates as a historical control. We will use standard parametric statistical analyses to determine change from pre-post surgery and referencing historical control data obtained from the literature. Multivariate statistical modelling will be considered for potential sources of confound if appropriate.

3. Provide a justification for the sample size used in this protocol.

Include the anticipated accrual rate, the accrual goal for the study, including accrual goals by strata if appropriate, adjustments for drop-outs etc. and study duration.

Answer/Response: ViviGen is already an FDA approved biologic, therefore a large sample size is not needed.

4. What is your plan for primary variable analysis?

Include a sketch of the analysis to assess primary study objectives.

Answer/Response: Radiographic evidence of successful arthrodesis confirmed on CT (defined by >50% fusion)

5. What is your plan for secondary variable analysis?

Include the following:
--A sketch of the analysis to assess secondary study objectives.
--For phase III studies, the power/precision of the study to address the secondary objective(s).

Answer/Response:

- Clinical & Radiographic evidence of failure (obvious non-union or hardware failure)
- Patient reported outcomes scores
- Vitamin D levels

6. Have you been working with a statistician in designing this protocol?

Answer/Response: No.

IF YES, what is their name?

Answer/Response:

7. Will data from multiple sites be combined during analysis?

Answer/Response: No.

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

Answer/Response:

IF YES, will randomization be done at each site or among sites?

Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?

Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Answer/Response:

7(d). Is there a common protocol used in all sites?

Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

INSTRUCTIONS:

This should include everything that will be done as part of this protocol. Do not repeat information that is included in other sections such as Background or Hypothesis sections.

This section should include an indication of which research interventions if any offer a prospect for direct benefit and which interventions (invasive measurements, collection of blood, tissue, data, surveys, etc.) are being done solely to answer a research question and generate generalizable knowledge. If the interventions done solely for research purposes are associated with greater than minimal risk they need to be justified. Describe and justify any control and experimental arm and include method, dose, and duration of drug administration. Reference any claim of clinical equipoise if applicable.

If you are obtaining specimens or data, provide information regarding the type of specimen/data, amount of specimen needed and how the specimen/data will be obtained and what analysis will be done with the specimen/data.

<u>Special note for studies with waiver of consent/waiver of documentation of consent:</u>
Include a statement regarding how subjects will be recruited. For other studies this information is captured in Recruitment does not need to be duplicated in this section.

Answer/Response: **All study visits will be performed when the patient comes in for clinical care**.

VISIT 1: SCREENING/BASELINE (will add about 45 minutes to your visit):

If you decide to be in this study, you will read and sign this consent form before any study related procedures take place. You will meet with the study doctor to determine if you are eligible and it is safe for you to participate in the study. This will include the following:

The following procedures will be done as **part of your clinical care** and recorded for research purposes in preparation for your arthrodesis surgery.

- Reviewing your medical history, including your smoking history and current alcohol use.
- Physical exam as well as your weight and height
- Review your current medications.
- If you are a female and able to have children, your physician will ask if you are pregnant and may perform a urine or serum pregnancy test to confirm that you are not pregnant.
- If you are not already currently taking Vitamin D supplements, it will be prescribed to you by your surgeon as part of your standard of care before surgery

The following procedures/assessment will be done **solely for research purposes:**

- Complete study questionnaires that will ask you about your level of pain, your daily activities, physical function, and quality of life. The questionnaires will take about 20 minutes to complete.
- Laboratory testing including collection of blood samples (1 ½ teaspoons)
    - Your blood will be analyzed to assess your Vitamin D levels

VISIT 2: SURGERY (as part of your clinical care) (will last about 2 ½ hours):

The following procedures will be done as **part of your clinical care** in preparation for your arthrodesis surgery. The results will also be recorded for research purposes:

- Recording of admission and surgical information from your medical chart
- Primary ankle or hindfoot arthrodesis using the ViviGen graft
- Surgical images of the hindfoot/ankle (intra-operative fluoroscopy and post-operative x-ray)

FOLLOW-UP (each visit will add about 45 minutes to your visit):

VISIT 3 –2 Weeks Post Surgery

The following procedures will be done as **part of your clinical care.** The results will be recorded for research purposes:

- Wound Check
- Physical assessment of the hindfoot/ankle, including vital signs

VISIT 4 - 6 Weeks Post Surgery

The following procedure will be done as **part of your clinical care.** The results will be recorded for research purposes:

- Physical assessment of the hindfoot/ankle, including vital signs
- X-rays of the hindfoot/ankle

VISITS 5, 6, and 7 –3 months, 6 months and 12 months Post-Surgery

The following procedures will be done as **part of your clinical care.** The results will be recorded for research purposes:

- Physical assessment of hindfoot/ankle, including vital signs
- X-rays of the hindfoot/ankle

The following procedures/assessment will be done **solely for research purposes:**

- Questionnaires
- Blood draw (1 ½ teaspoons) and analysis for Vitamin D levels (only at the 6 month visit)
- CT scan of your ankle/hindfoot

- ***At the conclusion of Visit #7, participation in the study is complete.***

2. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.

> **Example:** If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
> **Instructions:** Answer NA if this study does not involve a study treatment.

Answer/Response: N/A.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.** (e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)

Answer/Response: Study visits coincide with standard of care follow-up visits to their surgical procedure.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.** (e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)

Answer/Response: Subject misses 30% of study visits

Bibliography

1. Frey C, Halikus NM, Vu-Rose T, Ebramzadeh E. A review of ankle arthrodesis: predisposing factors to nonunion. Foot Ankle Int. 1994; 15(11):581-584.

2. Haddad SL, Coetzee JC, Estok R, et al. Intermediate and longterm outcomes of total ankle arthroplasty and ankle arthrodesis: a systematic review of the literature. J Bone Joint Surg Am. 2007;89(9):1899-1905.
3. K.L. Wapner. Triple arthrodesis in adults. J Am Acad Orthop Surg, 6 (1998), pp. 188–196
4. Burrus MT, Werner BC, Carr JB, Perumal V, Park JS. Increased Failure Rate of Modified Double Arthrodesis Compared With Triple Arthrodesis for Rigid Pes Planovalgus. J Foot Ankle Surg. 2016 Nov - Dec;55(6):1169-1174.
5. Daniels TR, Younger AS, Penner MJ, Wing KJ, Le IL, Russell IS, Lalonde KA, Evangelista PT, Quiton JD, Glazebrook M, DiGiovanni CW. Prospective Randomized Controlled Trial of Hindfoot and Ankle Fusions Treated With rhPDGF-BB in Combination With a β-TCP-Collagen Matrix. Foot Ankle Int. 2015 Jul;36(7):739-48.