BBOT: Bacterial Burden in Ortho Trauma Procedures

NCT03126448

Protocol Date: 19 Dec 2016

Approval Date: 10 Jan 2017

UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

Date: December 19, 2016

Print Close

View: v2_Introduction Page

Introduction Page

1 * Abbreviated Title:
Bacterial Burden in Ortho Trauma Procedures

2 * Full Title:
Prospective Evaluation of Bacterial Burden in Orthopaedic Trauma Procedures Using Highly Sensitive Assays

3

* Select Type of Submission:

- (●) **IRB Application**
- ( ) Humanitarian Use Device (for FDA approved Indication & non-research purposes ONLY)
- ( ) Emergency Use
- ( ) Unsure if this proposal requires IRB review (Not Human Subject Research)

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:

ID: VIEW4DF8709A33C00
Name: v2_Introduction Page

View: v2_Research Team Information

Research Team Information

1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Robert V. O'Toole

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, related to this research?
( ) Yes (●) **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Yasmin Degani

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, related to this research?
( ) Yes (●) **No**

3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

Name	Edit Submission	cc on Email	Research Role	Has SFI?
Aaron Johnson	no	no	Sub-Investigator	no
Manjari Joshi	no	no	Sub-Investigator	no

Name	Edit Submission	cc on Email	Research Role	Has SFI?
Andrea Howe	yes	yes	Research Team Member	no
Roman Natoli	yes	yes	Sub-Investigator	no
Brian De Palma	no	no	Sub-Investigator	no
Joshua Rudnicki	yes	no	Research Team Member	no

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

ID: VIEW4DF85C16F2800
Name: v2_Research Team Information

View: v2_Resources

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

1 * Describe the time that the Principal Investigator will devote to conducting and completing the research:
The PI will devote ample time to conducting and completing research.

2 * Describe the facilities where research procedures are conducted:
University of Maryland, Shock Trauma and UMMC Midtown Campus

3 * Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:
There are ample medical and psychological resources for all research subjects. In addition, there are plenty of qualified staff available for any questions regarding participating in research.

4 * Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:
All study staff have reviewed the protocol and research procedures so that they have a full understanding of the process of the study as well as their duties and functions.

ID: VIEW4DF83CB976400
Name: v2_Resources

View: v2_Sites Where Research Activities Will Be Conducted

Sites Where Research Activities Will Be Conducted

1 * Is this study a:
- (●) **Multi-Site**
- ( ) Single Site

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?
( ) Yes (●) **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?
( ) Yes (●) **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date
There are no items to display		

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)
( ) Yes (●) **No**

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general

oversight of conduct of the project)

○ Yes ○ No

6 * Institution(s) where the research activities will be performed:

- [ ] University of Maryland, The Founding Campus
- [ ] VAMHCS
- [ ] University of Maryland, Upper Chesapeake Kaufman Cancer Center
- [ ] UMB School of Medicine
- [ ] Marlene and Stewart Greenebaum Cancer Center
- [ ] University Physicians Inc.
- [x] **Shock Trauma Center**
- [ ] General Clinical Research Center (GCRC)
- [ ] Maryland Psychiatric Research Center (MPRC)
- [ ] Johns Hopkins
- [ ] International Sites
- [ ] UMB Dental Clinics
- [ ] Center for Vaccine Development
- [ ] Community Mental Health Centers
- [ ] Private Practice in the State of Maryland
- [ ] Institute of Human Virology (IHV) Clinical Research Unit
- [ ] Joslin Center
- [ ] UMB Student Classrooms
- [ ] National Institute of Drug Abuse (NIDA)
- [ ] National Study Center for Trauma and EMS
- [ ] Univ of MD Cardiology Physicians at Westminster
- [ ] Nursing Homes in Maryland
- [ ] University of Maryland Biotechnology Institute
- [ ] Department of Health and Mental Hygiene (DHMH)
- [ ] Mount Washington Pediatric Hospital
- [ ] Capitol Region PG Hospital
- [ ] Maryland Proton Treatment Center
- [ ] Other Sites
- [x] **University of Maryland Medical System (Select below)**

* UMMS Sites:

- [ ] University of Maryland Medical Center
- [x] **UMMC Midtown Campus (formerly Maryland General Hospital)**
- [ ] UM St. Joseph Medical Center
- [ ] UM Baltimore Washington Medical Center
- [ ] UM Charles Regional Medical Center
- [ ] UM Shore Medical Center at Easton
- [ ] UM Shore Medical Center at Chestertown
- [ ] UM Shore Medical Center at Dorchester
- [ ] UM Shore Emergency Center at Queenstown
- [ ] UM Shore Regional Health
- [ ] University of Maryland Rehabilitation & Orthopaedic Institute (formerly Kernan Hospital)
- [ ] UM Upper Chesapeake Health
- [ ] UM Upper Chesapeake Medical Center

- [ ] UM Harford Memorial Hospital
- [ ] University of Maryland Community Medical Group

ID: VIEW4DF870DF2C000
Name: v2_Sites Where Research Activities Will Be Conducted

View: v2_Funding Information

Funding Information

1 * Indicate who is funding the study:

- [ ] Federal
- [ ] Industry
- [x] **Department / Division / Internal**
- [ ] Foundation
- [ ] Private
- [ ] State Agency

2 * What portion of the research is being funded? (Choose all that apply)

- [ ] Drug
- [ ] Device
- [ ] Staff
- [ ] Participant Compensation
- [ ] Procedures
- [x] **Other**

3 Please discuss any additional information regarding funding below:

ID: VIEW4DF85DF452400
Name: v2_Funding Information

View: v2_Research Protocol

Research Protocol

1 * Do you have a research protocol to upload?

- ○ Yes
- ● **No, I do not have a research protocol and will use the CICERO application to enter my study information**

2 If Yes, upload the research protocol:

Name	Created	Modified Date

There are no items to display

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

View: v2_Risk Level

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

- (●) **Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.**
- ( ) Greater Than Minimal - Does not meet the definition of Minimal Risk.

ID: VIEW4E02805225800
Name: v2_Risk Level

View: v2_Type of Research

Type of Research

1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):

- [ ] Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.
- [ ] Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.
- [ ] Use of device(s) whose use is specified in the protocol
- [ ] Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).
- [x] **Sample (Specimen) Collection and/or Analysis (including genetic analysis).**
- [x] **Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).**
- [ ] None of the above.

2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

(●) **Yes** ( ) No

ID: VIEW4E0280569E000
Name: v2_Type of Research

View: v2_Lay Summary

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Infected broken bones that don't heal are a difficult clinical problem that significantly affect patient quality of life. Current methodology for detecting bacteria (growth in laboratory cultures) is inadequate to detect infections caused by bacteria existing in a biofilm, which is the layer of "slime" found in the presence of foreign bodies (eg, implanted metal devices to fix broken bones). Advances in molecular biology have allowed development of highly sensitive tests to detect bacteria in the biofilm state. However, the limited prior research has not included control groups or compared the performance of different highly sensitive tests. To address these limitations and further define the role of highly sensitive bacterial tests in clinical practice, we hypothesize that there will be increasing bacterial burden when comparing clean broken bone surgery (1st surgery) to implanted metal device removal (2nd surgery, bone healed) to index nonunion surgery (subsequent surgery, bone not healed) as measured by percentage of cases being positive for bacteria using highly sensitive bacterial tests. Further, the highly sensitive bacterial tests (Illumina MiSeq system and Ibis T5000 biosensor) will have similar ability to quantify the number of bacteria and differentiate bacterial species. Eligible patients will consist of three groups. Group 1 is clean broken bone surgery undergoing plate and screw fixation, intramedullary nailing fixation where the fracture site is accessible, or staged treatment of a broken bones initially treated by joint spanning external fixation device. Group 2 will include patients having a plate and screws removed without clinical evidence of infection. Group 3 will be patients undergoing an initial procedure for fracture nonunion. Tissue obtained at the time of surgery will be sent to the research laboratory for culture and performance of the two highly sensitive tests. The tissue samples taken will be tissue normally removed and discarded in the course of these particular procedures. The rates of positivity for culture and the highly sensitive tests will be compared amongst the three groups. We will also compare bacterial count and the distribution of bacterial species found using the two highly sensitive tests. These data will then undergo statistical analysis against clinical data gathered from review of the patients' charts. The overall project goal is to establish the clinical relevance of highly sensitive bacterial tests in diagnosing infected nonunions. The ability to more accurately identify patients with infection may lead to a change in clinical decision making with respect to surgical procedure or antibiotic treatment. This project will develop an improved understanding of the potential role of highly sensitive bacterial tests in diagnosing infected nonunions compared to the current standard of care, which is growing bacteria in the laboratory under artificial conditions.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

View: v2_Justification, Objective, & Research Design

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

The objective of this research is to see if highly sensitive bacterial assays are useful for determining whether fracture nonunions are infected? The following two

hypotheses will be tested:
1. There will be increasing bacterial burden when comparing clean index fracture surgery (1st surgery) to hardware removal (2nd surgery, bone healed) to index nonunion surgery (subsequent surgery, bone not healed) as measured by percentage of cases yielding a positive result using highly sensitive bacterial assays. Further, the highly sensitive bacterial assays will have a higher percentage of positive results compared to standard hospital culture based methods.
2. The highly sensitive bacterial assays Illumina MiSeq system and Ibis T5000 biosensor will have similar ability to semiquantify bacterial load and differentiate bacterial species for clean index fracture surgery (1st surgery), hardware removal (2nd surgery, bone healed), and index nonunion surgery (subsequent surgery, bone not healed).
The specific aims associated with each hypothesis is as follows:
Specific Aim #1: To establish baseline bacterial burden for common orthopaedic trauma procedures as measured by highly sensitive bacterial assays under modern perioperative antibiotic protocols and compare them to standard hospital culture based methods.
Specific Aim #2: To compare the ability of two highly sensitive bacterial assays (Illumina MiSeq system and Ibis T5000 biosensor) to semiquantify bacterial load and differentiate bacterial species in common orthopaedic trauma procedures.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

The study subjects will be patients who agree to participate in this prospective trial. Three groups of patients will be identified: 1) clean index fracture surgery (1st surgery), 2) hardware removal (2nd surgery, bone healed), and 3) index nonunion surgery (subsequent surgery, bone not healed). Specifically, group 1 will consist of closed fractures undergoing open reduction internal fixation (ORIF), intramedullary nailing (IMN) where the fracture site is accessible, or staged treatment of a pilon or plateau that was initially treated by joint spanning external fixation. Group 2 will include patients having a plate removed without clinical evidence of infection and excluding history of open fracture. Group 3 will be patients that are undergoing an index procedure for fracture nonunion. The definition of nonunion and indication for surgery will be at the discretion of the attending surgeon. Time from initial surgical treatment of the fracture to index nonunion surgery will be at least six months. There is not randomization as the study is a prospective observational design. Group 1, clean index fracture surgery, is the control group for this study. In order to make sure that patients do not have latent infections, patients who do not complete a 6-month standard follow-up with their surgeon in clinic will be contacted by phone. We will only seek to know if the patient has had any infections or complications since their surgery.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

Nonunions are a difficult clinical problem for both the patient and surgeon. Studies have shown that nonunion significantly decreases patients health related quality of life measures. There are several factors that may be responsible for fracture nonunion, one if which is infection. The presence of infection complicates the problem, with one third off of patients requiring additional procedures. From a clinical perspective, knowing the likelihood of infection preoperatively may lead to a change in plan (eg, choosing a type of procedure that does not place metal at the nonunion site). Additionally, an accurate diagnosis of the pathogenic bacteria will guide postoperative antibiotic decision making. Attempts have been made to improve the preoperative diagnosis of infection in patients undergoing nonunion surgery, but the gold standard remains purulence encountered at the time of surgery or identification of a bacterial species from culture of intraoperative specimens. Recent work calls into question the utility of culture based methods compared to highly sensitive assays for the detection of bacteria. This proposal seeks to further elucidate the relevance of highly sensitive assays for the detection of bacteria at fracture nonunion sites.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Bacteria exist in planktonic and biofilm forms. It is increasingly recognized that the biofilm form occurring in the presence of foreign material (eg, metallic implants) is the culprit biology in many orthopaedic infections. The current gold standard method for establishing the identity of the infecting organism is microbiologic laboratory culture. Unfortunately, culture is insufficient in ability to identify bacteria that exist in the biofilm state, partially due to the selection pressure posed by restrictive, artificial growth conditions. In fact, some bacterial species are not culturable. These issues reflect the bias of culture methodology. Additionally, several prior studies looking at orthopaedic procedures and hardware removals in patients without signs of infection have yielded positive culture results in up to 58% of cases, whereas culture results from patients undergoing nonunion surgery have ranged from ~12-37%. Clearly, the overlap in percent positive cultures from clinically seeming dissimilar groups makes interpretation of the data difficult, as some bacteria may be contaminant or commensal. Advances in molecular biology techniques have allowed the development of highly sensitive assays for detecting the presence of bacteria. Two recent studies compared culture positivity to positive results from highly sensitive assays for patients with open fractures and patients undergoing nonunion surgery. The highly sensitive techniques (Illumina MiSeq system and Ibis T5000 biosensor) were positive at a rate >3.6 times that of culture. This has led some to question whether the results of intraoperative cultures obtained during nonunion surgery should be trusted, particularly ones that are negative, as the culture methodology may not be picking up ‘occult/subclinical’ infections. This finding is akin to recent trends in the total joint arthroplasty literature. Again, many patients with suspected infected total joint replacements undergoing revision surgery are culture negative, but they are positive for bacteria when highly sensitive assays are employed. However, before adoption of highly sensitive assays in clinical practice, it is imperative to understand the unique facets and establish the clinical relevance of the results. As an example, in one study 5/7 (71%) of patients undergoing index total knee arthroplasty were positive using the Ibis T5000 biosensor, but only one of these patients went on to a revision surgery for infection, and the bacteria that was identified at revision surgery was different than that at index surgery. To further elucidate the role of highly sensitive bacterial assays in identifying infected nonunions, we propose a prospective evaluation of bacterial burden in routine orthopaedic trauma procedures. This will improve upon prior literature by including relevant control groups and comparing two highly sensitive assays ability to semiquantify bacterial load and differentiate bacterial species. Infected fracture nonunions are challenging clinical problems for both patient and surgeon. The ability to more accurately identify patients with infection may lead to a change in clinical decision making with respect to surgical procedure or antibiotic treatment. This project will develop an improved understanding of the potential role of highly sensitive bacterial assays in diagnosing infected nonunions compared to the current standard of care, microbiologic culture.

ID: VIEW4E02805EA0C00
Name: v2_Justification, Objective, & Research Design

View: v2_Supporting Literature

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the ‘Research Protocol’ page, cite the applicable section and page numbers from that document in the answer box below.***

1. Can we trust intraoperative culture results in nonunions? Palmer MP, Altman DT, Altman GT, Sewecke JJ, Ehrlich GD, Hu FZ, Nistico L, Melton-Kreft R, Gause TM 3rd, Costerton JW. J Orthop Trauma. 2014 Jul;28(7):384-90.
2. Preoperative diagnosis of infection in patients with nonunions. Stucken C, Olszewski DC, Creevy WR, Murakami AM, Tornetta P. J Bone Joint Surg Am. 2013 Aug 7;95(15):1409-12.
3. Management of infected nonunion of the long bones by a multidisciplinary team. Bose D, Kugan R, Stubbs D, McNally M. Bone Joint J. 2015 Jun;97-B(6):814-7.
4. The Fate of Patients with a "Surprise" Positive Culture After Nonunion Surgery. Olszewski D, Streubel PN, Stucken C, Ricci WM, Hoffmann MF, Jones CB, Sietsema DL, Tornetta P 3rd. J Orthop Trauma. 2015 Aug 8. [Epub ahead of print].
5. Time Trade-Off as a Measure of Health-Related Quality of Life: Long Bone Nonunions Have a Devastating Impact. Schottel PC, O'Connor DP, Brinker MR. J Bone Joint Surg Am. 2015 Sep 2;97(17):1406-10.
6. The devastating effects of tibial nonunion on health-related quality of life. Brinker MR, Hanus BD, Sen M, O'Connor DP. J Bone Joint Surg Am. 2013 Dec 18;95(24):2170-6.
7. Culture-independent pilot study of microbiota colonizing open fractures and association with severity, mechanism, location, and complication from presentation to early outpatient follow-up. Hannigan GD, Hodkinson BP, McGinnis K, Tyldsley AS, Anari JB, Horan AD, Grice EA, Mehta S. J Orthop Res. 2014 Apr;32(4):597-605.
8. The significance of positive cultures from orthopedic fixation devices in the absence of clinical infection. Moussa FW, Anglen JO, Gehrke JC, Christensen G, Simpson WA. Am J Orthop (Belle Mead NJ). 1997 Sep;26(9):617-20.
9. Bacterial colonization of orthopedic fixation devices in the absence of clinical infection. Dobbins JJ, Seligson D, Raff MJ. J Infect Dis. 1988 Jul;158(1):203-5.
10. Successful identification of pathogens by polymerase chain reaction (PCR)-based electron spray ionization time-of-flight mass spectrometry (ESI-TOF-MS) in culture-negative periprosthetic joint infection. Jacovides CL, Kreft R, Adeli B, Hozack B, Ehrlich GD, Parvizi J. J Bone Joint Surg Am. 2012 Dec 19;94(24):2247-54.
11. Infected nonunion of the long bones. Struijs PA, Poolman RW, Bhandari M. J Orthop Trauma. 2007 Aug;21(7):507-11.

12. Management of infected nonunion of long bones: the last decade (1996-2006). Motsitsi NS. Injury. 2008 Feb;39(2):155-60.
13. Novel Strategies for the Diagnosis of Posttraumatic Infections in Orthopaedic Trauma Patients. Firoozabadi R, Alton T, Wenke J. J Am Acad Orthop Surg. 2015 Jul;23(7):443-51.
14. New methods for the detection of orthopedic and other biofilm infections. Costerton JW, Post JC, Ehrlich GD, Hu FZ, Kreft R, Nistico L, Kathju S, Stoodley P, Hall-Stoodley L, Maale G, James G, Sotereanos N, DeMeo P. FEMS Immunol Med Microbiol. 2011 Mar;61(2):133-40.
15. Biofilm theory can guide the treatment of device-related orthopaedic infections. Costerton JW. Clin Orthop Relat Res. 2005 Aug;(437):7-11.
16. The importance of positive bacterial cultures of specimens obtained during clean orthopaedic operations. Dietz FR, Koontz FP, Found EM, Marsh JL. J Bone Joint Surg Am. 1991 Sep;73(8):1200-7.
17. Poor predictive value of broad-range PCR for the detection of arthroplasty infection in 92 cases. Panousis K, Grigoris P, Butcher I, Rana B, Reilly JH, Hamblen DL. Acta Orthop. 2005 Jun;76(3):341-6.
18. Histological assessment of the presence or absence of infection in fracture non-union. Simpson AH, Wood MK, Athanasou NA. Injury. 2002 Mar;33(2):151-5.
19. Experimental staphylococcal infections in the skin of man. Elek SD. Ann N Y Acad Sci. 1956 Aug 31;65(3):85-90.

2 If available, upload your applicable literature search:

Name	Created	Modified Date

There are no items to display

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

View: v2_Study Procedures

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:
There will be several patients requiring a single blood draw to obtain ESR, CRP, and WBC. It is standard of care for patients undergoing nonunion surgery to have these labs drawn prior to surgery. However, not every surgeon in our department draws these labs before hardware removal procedures. So, the one procedure being performed for research purposes only would be a one time blood draw to obtain ESR, CRP, and WBC from patients undergoing hardware removal that did not have one prior to surgery or the rare nonunion case that does not have these lab tests within one month prior to surgery. These blood draws would be performed on the day of surgery pre-operatively. The patient will not occur any additional needle sticks associated with these blood draws as they will already be receiving IV placement for anesthesia, and the blood tests would be drawn at the time of IV placement. The study will pay for any ESR, CRP, WBC obtained that the surgeon did not want as part of standard of care. At 6 months after surgery, many patients will have a standard of care follow-up with their surgeon. If this follow-up does not take place, we will contact these patients by phone to determine if they have experienced any infections or complications since their surgery.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):
The procedures being performed for treatment purposes are, 1. closed fractures undergoing open reduction internal fixation, intramedullary nailing where the fracture site is accessible, or staged treatment of a pilon or plateau fracture that was initially treated by joint spanning external fixation; 2. plate and screw removal; and 3. index procedure for fracture nonunion. In each of these surgical procedures tissue samples will be obtained for research culture and testing with highly sensitive bacterial assays. All of the tissue samples will come from tissue that would be debrided or discarded as part of the normal routine for that operation. Patients are normally advised to follow-up with their surgeon up to 6 months to 1 year after their surgery.

3 * Describe the duration of an individual participant's participation in the study:
From the day of surgery to 6 months from their surgery date when the patient is seen in clinic or contacted by phone.

4 * Describe the amount of time it will take to complete the entire study:
3 years

5 * Describe any additional participant requirements:
N/A

ID: VIEW4E0280585B400
Name: v2_Study Procedures

View: v2_Sample Size and Data Analysis

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:
The primary outcome from specific aim #1 is percentage of cases yielding a positive result. With three groups, there will be three comparisons: 1) clean index fracture surgery to hardware removal, 2) clean index fracture surgery to index nonunion surgery, and 3) hardware removal to index nonunion surgery. Using a Bonferroni correction starting at $p = 0.05$, α will be set at 0.016667. We will set the power at 0.8, or $\beta = 0.2$.

A prior work with the Ibis T5000 biosensor highly sensitive assay showed 88% of the nonunion cases were positive for bacteria. We will conservatively estimate 80% in

our series. We assume a 50% reduction in percentage of cases positive in the hardware removal group, yielding an estimate of 40% positive cases. For clean index fracture surgery, one would anticipate a low rate of percentage positive cases. However, given the highly sensitive nature of these assays, we will conservatively estimate 10% of the cases to be positive.
Using a standard estimation of sample size for comparing two binomial proportions (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html), 43 patients per group are required for comparison 1, 14 for comparison 2, and 30 for comparison 3. We will thus attempt to enroll 43 patients in the clean index fracture surgery and hardware removal groups and 30 patients in the index nonunion surgery group to be adequately powered to test the main hypothesis of specific aim #1 given the above stated assumptions.

In specific aim #2 the primary outcome is semiquantification of bacterial load, a continuous variable. The rate of clinical infection in clean index fracture surgery and hardware removal is low; in contrast, nonunions have a rate of at least 12.7% in larger patient cohorts. Based on there being 500 fold difference in number of Staphylococci needed to cause skin infection when a foreign body is present, a parametric power analysis comparing means amongst groups with a standard deviation equal to 20% of the mean (again using a Bonferroni correction starting at $p = 0.05$, $\alpha = 0.016667$, power at 0.8, $\beta = 0.2$) revealed that less than 30 patients were needed in all groups. Thus, our proposed sample size for specific aim #1 satisfies the number of patients needed to make the planned comparisons of specific aim #2. Additionally, the two recent studies comparing culture positivity to positive results from highly sensitive assays for patients with open fractures and patients undergoing nonunion surgery had 30 and 34 patients, respectively.

Based on CPT codes, review of clinical activity at our trauma center in the year prior to this proposal (July 2014-July 2015) showed 409 hardware removals and 56 nonunion surgeries on the tibia/fibula alone. Assuming a 20% refusal to participate rate, we would meet the proposed 30 patients in the nonunion group within one year. Of note, there were 51 additional nonunion procedures when including the clavicle, humerus, forearm, and femur from which we will be enrolling patients.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:
There will be three comparisons: 1) clean index fracture surgery to hardware removal, 2) clean index fracture surgery to index nonunion surgery, and 3) hardware removal to index nonunion surgery. The number of cases positive for bacteria in each of these groups will be compared against the others via comparing two binomial proportions. This is the primary outcome of specific aim #1. In specific aim #2, the outcome variable is bacterial count, and comparison of each group to the others will be a comparison of means. Additionally, though not part of the primary outcome power analysis, post-hoc testing beginning with univariate analysis will be used to look for any relationship between the clinically gathered data (eg, ESR, CRP, and WBC; patient demographics and comorbidities; injury characteristics; post-operative outcomes) and positivity for bacteria based on culture or the highly sensitive assays. Significant univariate variables will then be assessed via a multivariate analysis.

ID: VIEW4E02806052800
Name: v2_Sample Size and Data Analysis

View: v2_Sharing of Results

Sharing of Results

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:
No results will be shared.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

View: v2_Sample Collection/Analysis

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

1 * What type of samples will be involved in this study? (Check all that apply)
- [x] **Prospective (will be collected)**
- [ ] Existing (previously collected at the time of initial IRB submission)

2 * Will genetic analysis/testing be done on any of the samples?
○ Yes ● **No**

3 * Will this study involve banking of samples (storing for future research use)?
● **Yes** ○ No

4 * What is the purpose of the sample collection and/or analysis?
To be able to compare the proportion of cases positive for bacteria among three groups of orthopaedic patients using laboratory culture methods and highly sensitive bacterial assays.

5 * Is there the possibility that cell lines will be developed with any of the samples?
○ Yes ● **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?
○ Yes ● **No**

6.1 If Yes, give name(s) and affiliation(s):

7 * Will the sample material be sold or given to any third parties?
○ Yes ● **No**

7.1 If Yes, give name(s) and address(es):

ID: VIEW4E0E1A4B80000
Name: v2_Sample Collection/Analysis

View: v2_Prospective Samples

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

1 * What type of sample will be collected? (Check all that apply)
- ☑ **Blood**
- ☐ Bone Marrow Aspirate/Biopsy
- ☐ Cerebrospinal Fluid
- ☐ Saliva
- ☐ Skin
- ☐ Sputum
- ☐ Stool
- ☑ **Tissue**
- ☐ Tumor
- ☐ Urine
- ☐ Other

1.1 If Other, specify:

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:
Only a one time blood draw will be required. It will be ~2 tsps.

3 * What type of samples will be collected? (Check all that apply)
- ☑ **Leftover samples that were obtained for clinical purposes (no additional research procedures required)**
- ☐ Samples obtained specifically for research purposes-additional taken during a clinical procedure
- ☐ Commercial (for profit) samples
- ☑ **Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study**
- ☐ Other

3.1 If Other, specify:

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?
Unique code for each patient such that the samples will be blinded.

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
Samples will be held anonymously if the patient withdraws until analysis is complete.

8 * Will the samples be destroyed after the study is over?
○ Yes ● **No**

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.
Samples for the highly sensitive bacterial assays will be stored in a -80*C freezer in Dr. Shirtliff's laboratory for 5 years from completion of study enrollment.

ID: VIEW4E0E257D60C00
Name: v2_Prospective Samples

View: v2_Sample Banking

Sample Banking

You indicated that the study involves banking of samples (storing for future research use).

1 * Where will the sample(s) be banked? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number is was approved under.)
Dr. Shirtliff's lab.

2 * Does the banking institution have an approved policy for the distribution of samples?
○ Yes ● **No**

3 How long will the sample(s) be kept?

4 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

5 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

6 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
If a participant withdraws, the samples will be held anonymously.

7 * If the participant withdraws, explain how the data obtained from their sample(s) will be handled (e.g., will it be deleted?) ***(Please note that data for FDA regulated research cannot be deleted):***
If a participant withdraws, the data from their samples will be kept anonymously.

ID: VIEW4E0E7E82B5800
Name: v2_Sample Banking

View: v2_Data Collection / Record Review

Data Collection/Record Review

You indicated on the "Type of Research" page that your study involves data collection or record review (i.e., chart review, not self-report).

1 * What type of data will be collected/analyzed in this study? (Check all that apply)
☐ Retrospective/Secondary Analysis (data has already been collected at the time of initial IRB submission)
☑ **Prospective (data is not yet in existence and/or collected)**

2 * Will this study involve adding data to a registry or database for future use?
○ Yes ● **No**

3 * Will the data be released to anyone not listed as an investigator on the protocol?
○ Yes ● **No**

3.1 If Yes, give name(s) & affiliation(s):

ID: VIEW4E0E25A8CA400
Name: v2_Data Collection / Record Review

View: v2_Prospective Data

Prospective Data

You indicated that the study involves the collection of prospective data.

1 * Where is the data being collected from? (Check all that apply)

- [x] **Medical records**
- [x] **Medical images**
- [ ] Commercial (for profit) entity
- [ ] Publicly available records
- [ ] Schools
- [x] **Other**

1.1 If Other, please specify:
Blood tests and tissue samples as described above

2 * What data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.
We will need name, date of birth, MRN and telephone numbers for the purposes of this study. This information will be destroyed after data analysis is complete.

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date

There are no items to display

ID: VIEW4E0E25B643800
Name: v2_Prospective Data

View: v2_Clinical Trial Registration

Clinical Trial Registration

You indicated on the "Type of Research" page that your study is a clinical trial.

1 * Does the UM Clinical Trials Registry policy require registration of this trial?
○ Yes ● **No**

2 * Has this trial been registered?
● **Yes** ○ No

ID: VIEW4E093BF078C00
Name: v2_Clinical Trial Registration

View: v2_Clinical Trial Registration Information

Clinical Trial Registration Information

You indicated that this clinical trial has been registered.

1 * Was this trial registered at www.clinicaltrials.gov?
● **Yes** ○ No

2 If no, was this trial registered on a site other than clinicaltrials.gov?
○ Yes ○ No

2.1 If Yes, specify the name of the other site:

2.2 Provide justification for registering this trial on this site:

3 * Registration Number
NCT03126448

ID: VIEW4E093BF1D0800
Name: v2_Clinical Trial Registration Information

Participant Selection

1 * How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? ***Screening includes determining potential participants' initial eligibility for and/or interest in a study.***

750

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? ***A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.***

Local - the number being enrolled at this site:

300

Worldwide - the number being enrolled total at all sites (including local enrollment):

300

3 * Gender:

- [x] **Male**
- [x] **Female**

4 * Age(s):

- [ ] 0 to 27 days (newborn infants)
- [ ] 28 days to 12 months (Infant)
- [ ] 13 months to 23 months (Toddler)
- [ ] 2 to 5 years (Preschool)
- [ ] 6 to 11 years (Child)
- [ ] 12 to 17 (Adolescents)
- [x] **18 years and older (Adult)**
- [ ] 89 years and older

5 * Race/Ethnicity:

- [x] **All Races Included**
- [ ] American Indian or Alaskan Native
- [ ] Asian/Other Asian
- [ ] Asian/Vietnamese
- [ ] Black or African American
- [ ] Hispanic or Latino
- [ ] Mixed Race or Ethnicity
- [ ] Native Hawaiian or Pacific Islander
- [ ] White or Caucasian

6

* Language(s):

- [x] **English**
- [ ] Chinese
- [ ] French
- [ ] Italian
- [ ] Japanese
- [ ] Korean
- [ ] Local Dialect

- [ ] Spanish
- [ ] Vietnamese
- [ ] Other

6.1 Specify Other:

7 * Are you excluding a specific population, sub-group, or class?
○ Yes ● **No**

7.1 If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

ID: VIEW4E0E519C1D000
Name: v2_Participant Selection

View: v2_Vulnerable Populations

Vulnerable Populations

1 * Will you be targeting ANY of the following Vulnerable Populations for enrollment? (Select all that apply)

- [ ] Employees or Lab Personnel
- [ ] Children (Minors)
- [x] **Cognitively Impaired/ Impaired Decision Making Capacity**
- [ ] Pregnant Women/Fetuses
- [ ] Wards of the State
- [ ] Students
- [ ] Prisoners
- [ ] Nonviable Neonates or Neonates of Uncertain Viability
- [ ] Economically/Educationally Disadvantaged
- [ ] None of the above

Only select populations which you will be targeting for enrollment. Do not include populations that may be enrolled incidentally. Enrollment of a vulnerable population is considered to be "targeted" if the study team will be aware that a subject is from a vulnerable group as a result of interaction with the subject or collection of specific information about the subject, and the research team does not wish to exclude them. "Incidental" enrollment is limited to situations where a study team is unaware that a subject is from a vulnerable group.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

View: v2_Vulnerable Populations - Cognitively Impaired

Vulnerable Populations - Cognitively Impaired

You indicated that individuals who are cognitively impaired are included in this study.

1 * Describe how you will prevent undue coercion:
For these individuals we will obtain consent from a proxy/family member, or LAR. We will review the study, and consent forms, and use an Evaluation to Sign Consent Form asking questions based on the study to assess their full understanding and comprehension of what we are asking.

2 * How will the capacity of these individuals to provide informed consent be assessed? How will you determine the need for a legally authorized representative?
The research staff will endeavor to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol. A limited number of questions will be asked of all patients after they are introduced to the study and have reviewed the consent form. These questions assess the person's understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation.

The Research Coordinator will ask the questions and determine the appropriateness of the responses. If the Research Coordinator is at all unsure about the patient's ability to consent s/he will consult with the study site PI.

A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if the patient cannot adequately answer at least 2 questions and it is determined that the patient's level of cognition is not likely to change before surgery. An assent will not be obtained, but instead participants who are enrolled using a LAR will be re-consented when they are able to consent for themselves.

The choice of LAR will follow standard procedures. The following with be approached in this order of priority:
• Legal guardian
• Proxy (health care agent) named in an advance directive or durable power of attorney for health care;
• Family member or other surrogate identified by the state law on health care decisions.

Guidance will be provided to assist the LAR in making the consent decision. They will advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

You can also upload a copy of the tool that will be used to evaluate capacity:

Name	Created	Modified Date
Evaluation to Give Consent.docx	11/9/2015 8:43 AM	11/9/2015 8:43 AM

3 * From which participants, who are not able to provide legally effective informed consent, will assent be obtained?

- ○ All participants
- ○ Some participants
- ● **None of the participants**

ID: VIEW4E0E51976DC00
Name: v2_Vulnerable Populations - Cognitively Impaired

View: v2_Eligibility

Eligibility

1 * Do you have an existing Eligibility checklist(s) for this study?

○ Yes ● **No**

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
There are no items to display		

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Closed fracture undergoing open reduction internal fixation, intramedullary nailing (IMN) where the fracture site is accessible, or staged treatment of a pilon or plateau that was initially treated by joint spanning external fixation
View	2	Plate and screw removal without clinical evidence of infection
View	3	Index procedure for fracture nonunion

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Index fracture surgery for an open fracture or intramedullary nailing with fracture site not accessible
View	2	Hardware removal if fracture not already healed
View	3	Index nonunion surgery being bone grafting of a 'critical' defect
View	4	Pregnant females

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00066769_1 v11-17-2015-1447774904227(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

View: v2_Recruitment

Recruitment

1 * Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):
All orthopaedic patients are discussed in morning conference. This is standard of care. All research team members study will evaluate the current population and trauma admissions for eligible patients. Once eligibility is confirmed, a member of the research team will initiate the research consent conversation.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter "N/A"):
Patients will be reminded that study participation is voluntary, and that the decision to participate or not, will not alter the care they receive in any way.

3 * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)
- [x] **PI**
- [x] **Study Staff**
- [ ] Third Party

3.1 If you are using a third party, specify Third Party Recruiters:

4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date

There are no items to display

ID: VIEW4E0BCAA0A6C00
Name: v2_Recruitment

View: v2_Advertising

Advertising

1 * Will you be using advertisements to recruit potential participants?
○ Yes ● **No**

ID: VIEW4E0BCCF811000
Name: v2_Advertising

View: v2_Research Related Risks

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1 * Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:
Blood draw - risk of further bleeding and site infection. Minimal risk. Unlikely that the patient will experience complications as it will be drawn on the day of surgery as the IV is placed for anesthesia.
Safety issues related to this are only concerns related to patient privacy.
There is a slight risk of a breach of confidentiality since there will be PHI accessed and recorded for the study however we will try to minimize this by maintaining password-protected databases.

ID: VIEW4E1B52509F000
Name: v2_Research Related Risks

View: v2_Potential Benefits and Alternatives

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the potential direct benefit(s) to participants:
While there are no direct benefits to patients participating in the study, participation may help determine if highly sensitive bacterial assays are useful in determining if fracture nonunions are infected.

2 * Describe the importance of the knowledge expected to result from the study:
The ability to more accurately identify patients with infection may lead to a change in clinical decision making with respect to surgical procedure or antibiotic treatment.

This project will develop an improved understanding of the potential role of highly sensitive bacterial assays in diagnosing infected nonunions compared to the current standard of care, microbiologic culture.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:
The breach of confidentiality is minimal. The benefits of properly identifying infected nonunions and treating them to improve patient quality of life and minimize the need for further reconstructive procedures will have a much more profound and positive effect.

4 * Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.
Participation is voluntary; the alternative is not to participate.

ID: VIEW4E1B5251B0400
Name: v2_Potential Benefits and Alternatives

View: v2_Withdrawal of Participants

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 * Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:
Patients will be withdrawn if the study is ended early, if the PI decides it is no longer in the subject's best interest, or for other reasons.

2 * Describe procedures for orderly termination:
N/A

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:
Patient data already collected will be maintained for analysis with the remainder of the research pool.

ID: VIEW4E1B52531F800
Name: v2_Withdrawal of Participants

View: v2_Privacy of Participants

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 * Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***
It is the Investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission. Patients will be identified only by identification code but not by their name, SSN, or hospital medical record number. The investigator will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses (i.e., available only to local clinic staff). All study material will be maintained in strict confidence. All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentialiy. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Consent procedures and forms, and the communication, transmission and storage of patient daata will comply with individual site IRB requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:
Potential participants could receive information in the trauma resuscitation unit (TRU: Admitting area) or on the floor. In either case there will be a curtain to draw for privacy or a private room where a door can be closed.

3 * Describe potential environmental stressors that may be associated with the research:
No potential environmental stressors that may be associated with the research.

4 * Will this study have a site based in the European Union?
○ Yes ● **No**

5 * Will the study have planned recruitment or data collection from participants while they are located in the European Union?
○ Yes ● **No**

Access link below for information about the EU General Data Protection Regulations to assist in answering these questions.
https://www.umaryland.edu/oac/general-data-protection-regulation/

ID: VIEW4E1B525B87C00
Name: v2_Privacy of Participants

View: v2_Confidentiality of Data

Confidentiality of Data

1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

- (●) **Yes**
- ( ) No, the data will be stored de-identified/anonymous (stripped of all identifiers, no way to identify individual participants)

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

3 * How will such data be secured?

All data will be password protected and locked in an office to which there is limited access.

4 * Who will have access to research data?

Approved research staff and PI

5 * Will study data or test results be recorded in the participant's medical records?

( ) Yes (●) **No**

6 * Will any data be destroyed? ***(Please note that data for FDA regulated research and VA research cannot be deleted)***

( ) Yes (●) **No**

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

7 Do you plan to obtain a Certificate of Confidentiality?

( ) Yes (●) **No**

7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name	Created	Modified Date

There are no items to display

8 * Discuss any other potential confidentiality issues related to this study:

N/A

ID: VIEW4E1B5265E0400
Name: v2_Confidentiality of Data

View: v2_Monitoring Plan Selection

Monitoring Plan Selection

1 * Type of data safety monitoring plan for the study:

- ( ) Will use/defer to the external sponsor's Data Safety Monitoring Plan
- ( ) Data Safety Monitoring by a Committee
- (●) **Data Safety Monitoring by an Individual**
- ( ) There is no data safety monitoring plan in place

ID: VIEW4E1B00E30D400
Name: v2_Monitoring Plan Selection

View: v2_Monitoring Plan - Individual

Monitoring Plan - Individual

You indicated that the monitoring will be done by an Individual.

1 * Identify the individual who will be performing the safety monitoring:
Robert V. O'Toole, MD

2 * Describe this individual's role in relation to the protocol:
PI

3 * What data will be reviewed?
- [x] **Adverse Events**
- [x] **Enrollment Numbers**
- [x] **Patient Charts/Clinical Summaries**
- [x] **Laboratory Tests**
- [ ] Medical Compliance
- [ ] Procedure Reports
- [ ] Raw Data
- [x] **Outcomes (Primary, Secondary)**
- [x] **Preliminary Analyses**
- [ ] Other

3.1 If Other, specify:

4 * What will be the frequency of the review?
- (●) **Annually**
- ( ) Bi-Annually
- ( ) Other

4.1 If Other, specify:

5 * Safety monitoring results will be reported to:
- [x] **IRB**
- [ ] GCRC
- [ ] Sponsor
- [ ] Other

5.1 If Other, specify:

ID: VIEW4E1B026A2A400
Name: v2_Monitoring Plan - Individual

View: v2_Research Related Costs

Research-Related Costs

1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?
- (●) **No**
- ( ) Yes

1.1 If Yes, check all that apply:
- [ ] Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)
- [ ] Investigational or Study Device
- [ ] Investigational or Study Drug

☐ Investigational Procedure(s)

1.2 If No, who is responsible for payment?
There are no research-related costs

2 * Who is responsible for the uncovered research-related costs?

- ☐ Participant
- ☐ Sponsor
- ☐ UM
- ☐ Other
- ☑ **There will be no uncovered research-related costs**

2.1 If Other, specify:

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

ID: VIEW4E1B5D9641800
Name: v2_Research Related Costs

View: v2_Compensation for Research-Related Injury

Compensation for Research-Related Injury

1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

○ Yes ● **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date

There are no items to display

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

○ Yes ● **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date

There are no items to display

ID: VIEW4E1B629EEC000
Name: v2_Compensation for Research-Related Injury

View: v2_Payment to Participants

Payment/Reimbursement to Participants

1 * Will participants receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research?

○ Yes ● **No**

ID: VIEW4E1C52A5D7800
Name: v2_Payment to Participants

View: v2_HIPAA

HIPAA (Health Insurance Portability and Accountability Act)

1 * HIPAA applies to the University of Maryland School of Medicine, the University of Maryland School of Dentistry and the VA.

Are you affiliated with, or will be accessing data from, any of these places? ● **Yes** ○ No

2 If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA? ● **Yes** ○ No

ID: VIEW4E1B0A2114400
Name: v2_HIPAA

View: v2_Protected Health Information

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

1 * Which PHI elements will be used or disclosed in this study? (Check all that apply)

- [x] **Name**
- [ ] Address (if more specific than Zip Code)
- [x] **Dates**
- [ ] Ages over age 89
- [x] **Telephone numbers**
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security numbers
- [x] **Medical record numbers**
- [ ] Health plan beneficiary numbers
- [ ] Account numbers
- [ ] Certificate/license numbers
- [ ] Vehicle identifiers and serial numbers, including license plate numbers
- [ ] Device identifiers and serial numbers
- [ ] Web universal resource locators (URLs)
- [ ] Internet protocol (IP) address numbers
- [ ] Biometric identifiers, including fingerprints and voiceprints
- [ ] Full-face photographic images and any comparable images
- [ ] Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification
- [ ] None

2 * Why is the PHI necessary for this research?
If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits).
The PHI is necessary for this research in order to access medical records.

3 * What is the source(s) of the PHI?
Medical Record

4 * Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).
The PHI will not be reused

5 * How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply:)

- [x] **Obtain written authorization** ***(upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms")***
- [x] **Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)**
- [ ] Qualifies as a limited data set (LDS)

5.1 If you are using a limited data set (LDS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E1B0A24AA400
Name: v2_Protected Health Information

View: v2_Waiver/Alteration of Authorization

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

1 * Provide rationale for how the research presents no more than minimal risk to the privacy of individuals:
Data stored in password-protected file on password-protected computer. Research subjects will be assigned a unique study ID to further reduce the chances for the release of PHI.

2 * Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:
Research subjects will be assigned a unique study ID to reduce the chances for the release of PHI.

3 * Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:
PHI collected for this study will be eliminated after initial data analysis.

4 * Why could the research not practicably be done without access to and use of this PHI?
We will need to have access to the patient's name and MRN prior to recruitment in order to determine their eligibility for the study. We would not be able to enroll without this. Phone numbers are necessary to follow up with patients that will not come back in to the clinic for a standard visit. A HIPAA waiver is being sought for these purposes.

5 * Why could the research not practicably be done without the waiver or alteration?
We will need to have access to the patient's name and MRN prior to recruitment in order to determine their eligibility for the study. We would not be able to enroll without this. Phone numbers are necessary to follow up with patients that will not come back in to the clinic for a standard visit. A HIPAA waiver is being sought for these purposes.

6 * Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?
○ Yes ● **No**

6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.

ID: VIEW4E1B0A2896400
Name: v2_Waiver/Alteration of Authorization

View: v2_Informed Consent Process

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/A" to the questions below.

1 * Indicate the type(s) of consent that will be involved in this study: (check all that apply)

- ☐ Not applicable (study may qualify as exempt)
- ☐ Request to Waive Consent/Parental Permission (Consent is not being obtained)
- ☐ Request to Alter Consent (Some Elements of Consent Waived)
- ☐ Request to Waive Documentation of Consent (Verbal/Oral Consent)
- ☑ **Written Consent Form**
- ☐ Electronic Consent

2 * Describe the Informed Consent process in detail:
To encourage a high level of participation from eligible patients, the attending surgeon will be involved in the consent conversation. The conversation will be initiated by a member of the research team and/or the surgeon together. Patients will be informed of the study and intended use of blood samples obtained and any relevant data that will be collected or analyzed in conjunction with the study. Patients and their families will be provided with copies of the consent form describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate.

3 Confirm that the consent process will explain the following:

- The activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

* ● **Yes** ○ No

4 * Describe who will obtain Informed Consent:
Research Team Member

5 * If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. *(Answer "N/A" if not obtaining consent from LARs)*
LAR will be confirmed by providing ID.

6 * Describe the setting for consent:
All interaction will occur in private patient areas where curtains can be drawn or doors closed.

7 * Describe the provisions for assessing participant understanding:
The research staff will endeavor to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol. A limited number of questions will be asked of all patients after they are introduced to the study and have reviewed the consent form.

The research staff will ask the questions and determine the appropriateness of the responses. If the research team member is at all unsure about the patient's ability to consent s/he will consult with the study site PI.

The choice of LAR will follow standard procedures. The following with be approached in this order of priority:
• Legal guardian
• Proxy (health care agent) named in an advance directive or durable power of attorney for health care;
• Family member or other surrogate identified by the state law on health care decisions.

8 * Describe the consideration for ongoing consent:
Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

ID: VIEW4E1C661D0AC00
Name: v2_Informed Consent Process

View: v2_Consent Forms - Draft

Consent and HIPAA Authorization Forms - Draft

1 Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
Consent 66769.doc	10/6/2015 12:56 PM	1/6/2017 3:23 PM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

1A Archived Consent Forms:

Name	Created	Modified Date
There are no items to display		

2 Upload any HIPAA authorization forms here:

HIPAA 66769.doc	10/6/2015 12:57 PM	11/9/2015 9:05 AM

Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates:
http://hrpo.umaryland.edu/researchers/consents.html

ID: VIEW4E1C7712D3000
Name: v2_Consent Forms - Draft

View: v2_Organization Review Requirements (other than IRB)

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

Orthopedics

If this information is incorrect, please notify the HRPO office.

2 **RSC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation? ○ Yes ● **No**

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer? ○ Yes ● **No**
-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required.

* Does the protocol involve in any way studies related to the prevention, treatment, diagnosis, or imaging of neoplastic diseases? ○ Yes ● **No**

5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient-oriented research. Click Here for more information.

Answer the following to determine if review by the GCRC may be required.

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? ○ Yes ● **No**

6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

* 6.1 - Will the research be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments)? ○ Yes ● **No**

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? ○ Yes ● **No**

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? ○ Yes ● **No**

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

ID: VIEW4E1AF91AB2400
Name: v2_Organization Review Requirements (other than IRB)

View: v2_Summary of Required Reviews (other than IRB)

Summary of Required Reviews (other than IRB)

1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission

This protocol has no related submissions (RSC, GCRC, IBC, etc)

2 **Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study

team are required.

Name of Organization	Review Status
Orthopedics	Complete
SOM Program in Trauma	Complete

ID: VIEW4E1C8D9AE4000
Name: v2_Summary of Required Reviews (other than IRB)

View: v2_Additional Documents

Additional Documents

1

Upload all additional documents here:

Name	Created	Modified Date
BBOT 6-month Phone Script.doc	1/6/2017 3:15 PM	1/6/2017 3:15 PM
HIPPA certificates Gitajn.docx	11/9/2015 8:24 AM	11/9/2015 8:24 AM

ID: VIEW4E0962513A000
Name: v2_Additional Documents

View: v2_Final Page of Application

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
Orthopedics	Complete
SOM Program in Trauma	Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission

This protocol has no related submissions (RSC, GCRC, IBC, etc)

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation
By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- If Required, obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

Click the "Finish" button and then click "Submit Application" in the submission Workspace.

ID: VIEW4E1B10C500000
Name: v2_Final Page of Application

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Aaron Johnson

2 Research Role:

Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
○ Yes ● **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Experienced in conducting research and has excellent knowledge of the local study sites, culture, and society.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Manjari Joshi

2 Research Role:
Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
○ Yes ● **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Very experienced in conducting research and has good knowledge of local study sites, culture, and society.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Andrea Howe

2 Research Role:

Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Very experienced in conducting research and has good knowledge of the local study site

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Roman Natoli

2 Research Role:
Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
● **Yes** ○ No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Very experienced in conducting research and has good knowledge of the local study site

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Brian De Palma

2 Research Role:

Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
○ Yes ● **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
○ Yes ● **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Very experienced in conducting research and has local knowledge of the local study sites, culture, and society.

View: IRB - Add a Team Member

Add a Team Member

1 * Select Team Member:
Joshua Rudnicki

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
● **Yes** ○ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
○ Yes ● **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Experienced in conducting research and has excellent knowledge of the local study sites, culture, and society.