

Comparing Ankle Arthrodesis to Ankle Arthroplasty

Manual of Operations and Procedures

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Table of Contents

Abbreviations Used in the MOOP.....	6
1.0 INTRODUCTION TO THE MANUAL OF OPERATIONS AND PROCEDURES (MOOP).....	7
2.0 STUDY OVERVIEW.....	7
3.0 MOOP CONTENTS AND ORGANIZATION.....	8
3.a Study Protocol.....	8
3.b Schedule of Visits and Evaluations.....	18
3.c Study Flow.....	19
3.d Study Organization and Responsibilities.....	21
3.d.1 Roster.....	21
3.d.2 Coordinating Center.....	27
3.d.3 Clinical Sites.....	28
3.d.4 Pharmacy Activities (N/A).....	31
3.d.5 Steering Committees.....	31
3.d.6 Executive Committees (N/A).....	31
3.e Training Plan.....	31
3.f Communications Plan.....	32
3.g Recruitment, Screening, and Eligibility Criteria.....	32
3.g.1 Recruitment Plan.....	32
3.g.2 Screening.....	33
3.g.3 Screening Log.....	33
3.g.4 Eligibility Criteria.....	34
3.h Informed Consent and HIPAA.....	34
3.h.1 Informed Consent Process.....	34
3.h.2 Informed Consent Document.....	35
3.h.3 HIPAA Authorization.....	35
3. i Treatment Allocation.....	35

- 3.j.1 Blinding and Unblinding (Not applicable).....36
- 3.k Study Intervention.....36
- 3.l Participant Evaluations and Follow-Up.....37
 - 3.l.1 Timeline and Visit Schedule.....37
 - 3.l.2 Scope.....38
 - 3.l.3 Follow-up.....39
 - 3.l.4 Follow-Up Data Collection using Redcap.....40
- 3.m Participant Retention.....41
- 3.n Concomitant Medications.....42
 - 3.n.1 Safety Reporting.....42
 - 3.n.2 Adverse Event Reporting.....43
 - 3.n.3 Serious Adverse Event Reporting.....43
 - 3.N.4 Adverse Event Reporting Requirements.....44
- 3.o Data and Safety Monitoring Activities.....44
 - 3.o.1 Generic Monitoring Plans.....45
 - 3.o.2 Safety Officer and DSMB Membership.....45
- 3.p Study Compliance.....45
- 3.q Source Documentation.....45
 - 3.q.1 Study Forms.....46
 - 3.q.2 General Instructions for Completing Forms.....46
- 3.r Data Flow.....47
- 3.s Retention of Study Documentation.....48
- 3.t Administrative Forms.....49
- 3.u Data Management.....49
- 3.v Quality Control Procedures.....51
 - 3.v.1 Double Data Entry.....51
 - 3.v.2 Site Monitoring.....51

3.w Reports.....	52
3.x Study Completion and Closeout Procedures.....	52
3.x.1 Participant Notification.....	54
3.y Policies.....	54
3.y.1 Confidentiality Procedures.....	54
3.y.2 Publications.....	55
3.z MOOP Maintenance.....	56
4.0 RELEVANT WEBSITES.....	56
5.0 FIGURES.....	57
Figure 1:.....	57
Figure 2:.....	57
Figure 3:.....	58
Figure 4:.....	59
6.0 LIST OF APPENDICES.....	60
7.0 REFERENCES.....	61

ABBREVIATIONS USED IN THE MOOP

AAOS The American Academy of Orthopaedic Surgeons

AE	Adverse Event
AOFAS	The American Orthopaedic Foot and Ankle Society
BMI	Body Mass Index
CITI	Collaborative Institutional Training Initiative
CPG	Chronic Pain Grade
CRF	Case Report Form
DCF	Data Clarification Form
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
ESAA	End Stage Ankle Arthritis
FAAM	Foot and Ankle Ability Measure
FCI	Functional Comorbidity Index
GCP	Good Clinical Practice
HIPAA	The Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IRB	Institutional Review Board
MOOP	Manual of Operations and Procedures
ITHS	Institute of Translational Health Sciences
NIAMS	The National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	The National Institutes of Health
OA	Osteoarthritis
PLTOP	Patient Long-Term Outcome Priorities
PI	Principal Investigator
PM	Project Manager
RCT	Randomized Controlled Trial
RR&D	Rehabilitation Research & Development (VA Center for Limb Loss Prevention & Prosthetic Engineering)
SAE	Serious Adverse Event
SAM	StepWatch™ Activity Monitor
SF-36	Short Form (36) Health Survey
SIBCR	The Seattle Institute for Biomedical and Clinical Research
SOP	Standard Operating Procedure
SQL	Structured Query Language
UAE	Unexpected Adverse Event
UAP	Unanticipated Problem
VAPSHCS	VA Puget Sound Health Care System

1.0 INTRODUCTION TO THE MANUAL OF OPERATIONS AND PROCEDURES (MOOP)

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and National Institutes of Health (NIH) must ensure compliance with Federal laws and regulations, including procedures and policies to protect the safety of all participants in the clinical studies it supports. A MOOP is a handbook that transforms the study protocol into guidelines that describe study organization, operational data definitions, recruitment, screening, enrollment, randomization, follow-up procedures, data collection methods, data flow, Case Report Forms (CRFs), and quality control procedures. The role of the MOOP is

to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Use of the MOOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that patient safety and scientific integrity are closely monitored.

2.0 STUDY OVERVIEW

The purpose of this research is to compare arthrodesis with arthroplasty in the treatment of end stage ankle arthritis (ESAA). The absence of this comparative outcome information is crippling the development of clinical guidelines. The American Academy of Orthopaedic Surgeons (AAOS) abandoned plans this year to publish clinical guidelines for treatment of ankle arthritis because of a lack of evidence. Arthrodesis is considered the primary/gold standard treatment in the absence of evidence or quality functional outcome data due to the historical lack of an acceptable surgical alternative. Currently, the treatment selection is based on the training and preference of the surgeon, and the preference of the patient. Only a few prospective cohort studies have compared the safety and efficacy of these treatment options, and no Randomized Controlled Trials (RCTs) have been published. Now that a respectable treatment alternative to arthrodesis is available, an RCT is the next logical step, and the study team attempted a modified RCT design called a Comprehensive Cohort Design from study inception in May 2012 until February 2014. At the recommendation of the NIAMS, efforts to randomize patients to arthrodesis or arthroplasty stopped due to a lack of patient willingness to randomize. The experimental focus of this research remains two-fold: 1) to compare arthrodesis and arthroplasty treatment outcomes in similar patient populations and 2) to identify intrinsic and extrinsic prognostic factors of arthroplasty patients with successful and unsuccessful outcomes for the purpose of establishing clinical indications and contraindications for arthroplasty. This will be accomplished by measuring pain, ankle function, general health, patient satisfaction, and physical activity based on step counts at 3, 6, 12, and 24 months after surgery in a multi-site prospective cohort study. Additional annual follow-ups, for up to 20 years, measuring pain, ankle function, general health, secondary surgery and patient satisfaction will also be used to assess long term outcomes; these follow-ups will be conducted as long as we are able to support them. To meet the enhanced numbers required to power for a prospective cohort study, this study has six participating sites. To assure parity in surgical skill in both treatments, we employ only surgeons with a minimum 5 years of experience and performance of at least 30 total ankle replacements and 30 ankle fusions. Though there are many issues that can only be answered by a longer study, we expect to answer our stated aims within this follow-up.

3.0 MOOP CONTENTS AND ORGANIZATION

3.A STUDY PROTOCOL

Study Introduction

The majority of clinical and basic science research of osteoarthritis (OA) has focused on the hip and the knee, with the ankle joint receiving considerably less attention even though arthritis of the ankle is of equal or greater impact.^{1,2,3} Ankle arthritis is estimated to occur in 6% of the general population⁴, with a smaller proportion of these individuals presenting with ESAA requiring surgical intervention, the

prevalence of which is unknown. ESAA is also more likely to be post-traumatic⁴, and it affects younger people⁵. Arthrodesis has, until recently, been regarded as the primary/gold standard treatment in the presence of ESAA and failure of conservative management⁶. Historically, this is in part due to the lack of an acceptable surgical alternative conducive to prospective comparison studies. However, major modifications in the design and techniques of arthroplasties have challenged the assumption of arthrodesis as the primary treatment.^{7,8,9} Moreover, few patients accept ankle fusion without reservation; this limits the clinical value of arthrodesis and leaves an obvious need for alternative treatment choices¹⁰. There are dozens of published case series on ankle arthrodesis and ankle arthroplasty, but only a few direct comparison studies,^{11,12,13} and no large RCTs. This is troubling given the plethora of comparative studies – both well designed cohort and RCTs – found in the total hip and knee literature. This study was originally designed as a multi-site RCT comparing ankle arthrodesis to ankle arthroplasty. Since some patients have a strong surgical preference, the original study design also allowed enrollment into a preference cohort using a modified Comprehensive Cohort Design. The NIAMS recommended stopping all efforts to enroll patients into the randomized cohort after February 2014 due to a lack of patient interest in randomization, so now the study follows a prospective cohort design. No patients elected randomization prior to February 2014.

The purpose of this study is to compare ankle arthroplasty and ankle arthrodesis for treatment of ESAA. The experimental focus of this research is two-fold: 1) to compare arthrodesis vs. arthroplasty treatment outcomes in similar patient populations and 2) to identify intrinsic and extrinsic prognostic factors of arthroplasty patients with successful and unsuccessful outcomes for the purpose of establishing clinical indications and contraindications for arthroplasty. The primary and secondary specific aims for this funding period are designed to answer these objectives and other important secondary clinical objectives over a 2-year follow-up. We intend to pursue additional and subsequent funding to extend this research for up to 20 years.

Primary Specific Aims

- 1) Compare overall physical function and ankle specific function between subjects undergoing ankle arthrodesis and total ankle arthroplasty at 3, 6, 12, and 24 months. Additional annual comparison data may be collected.
- 2) Compare overall ankle pain intensity and interference with activities in subjects undergoing ankle arthrodesis and total ankle arthroplasty at 3, 6, 12, and 24 months. Additional annual comparison data may be collected.
- 3) Compare overall general health in subjects undergoing ankle arthrodesis and total ankle arthroplasty at 3, 6, 12, and 24 months. Additional annual comparison data may be collected.

Secondary Specific Aims

- 1) Identify intrinsic and extrinsic prognostic factors which are predictive of higher physical function, ankle specific function, reduced pain, improved general health, and overall patient satisfaction.
- 2) Compare post-surgical complication rates.
- 3) Compare step counts pre-operatively and at 6, 12, and 24 months.
- 4) Compare patient satisfaction at 3, 6, 12 and 24 months. Additional annual comparison data may be collected.

Study Sites

The six participating sites include the VA Rehabilitation Research and Development Center for Limb Loss Prevention and Prosthetic Engineering (VA Puget Sound Health Care System; Seattle, WA), Harborview Medical Center (Seattle, WA), Orthopaedic Associates of Michigan (Grand Rapids, MI), Orthopedic and Fracture Specialists (Portland, OR), Twin Cities Orthopedics (Edina, MN), and Orthopaedic and Spine Center of the Rockies (Fort Collins, CO). The grant is administered through the Seattle Institute for Biomedical and Clinical Research (SIBCR). SIBCR is a non-profit organization that works with the VA to conduct federally-funded clinical research. The VA Puget Sound Health Care System (VAPSHCS) also functions as the Coordinating Center for the study.

Study Design

This is a multi-site prospective cohort study to compare ankle arthroplasty to ankle arthrodesis in the treatment of ESAA. This design allows us to include all subjects who are clinical candidates for either treatment (Figure 1). We previously attempted to enroll and randomize patients via a modified Comprehensive Cohort Design but efforts to randomize patients failed due to preconceived preferences and reluctance to randomly select a major, non-experimental, surgical procedure. Our current design may provide additional advantages, such as increased subject enrollment and retention.

A maximum of two groups will be used in this design: subjects who are clinical candidates for either surgery, but elect to have arthroplasty or arthrodesis.

Patient Population Eligibility Criteria

All subjects presenting to the orthopedic surgical clinics at each participating site who have failed non-surgical care for ankle arthritis and who have decided in consultation with their physician that surgery is the best option will be asked to participate. Participating sites will identify eligible patients who meet the study criteria prior to surgery. Physicians at participating sites will inform potential subjects about the study during a clinic visit. A study coordinator trained for this study will meet with potential subjects to determine their eligibility and interest in the study. This discussion will include a series of questions to confirm eligibility, a description of the study, and the responsibilities and potential risks and benefits of participation. Study aids focused for study education and support will include an overview of the study, a brochure about volunteering in research, and contact numbers in the event of complications or questions regarding study procedures and follow-up visits. Study sites may also use other IRB-approved recruitment materials such as brochures, fliers, and handouts. Upon patient agreement, eligibility will be verified based on inclusion/exclusion criteria, the study coordinator will initiate the informed consent process and note the treatment group selected. We originally estimated that a total of 512 patients will be enrolled in this study over a 30 month period. At the request of the NIAMS and DSMB, we conducted a conditional power analysis to determine if additional patients will be needed for statistical significance. Results from October 2014 indicated our sample size would be sufficient. Detailed enrollment information per-site can be found in Table 1. Sites may be approved for enrollment beyond the numbers listed; exact approval for number of enrolled subjects is found in each site’s IRB approval letter.

Table 1: Expected sample size by participating site.

Sites	Estimated	Enroll	Complete [†] 24-mo Follow-up
TOTAL	910	512	462

Seattle (WA)	250	141	127
Portland (OR)	60	34	31
Grand Rapids (MI)	150	84	76
Edina (MN)	300	169	152
Fort Collins (CO)	150	84	76

*Based on annual surgeries for 5 facilities (Seattle includes both the VA and Harborview) with a 30-month recruitment period.

**Based on a 75% eligibility rate and 75% of those eligible willing to participate.

† Based on a 10% loss to follow-up rate (n=53) and includes all subjects. VA RR&D just completed a multisite prospective trial of dysvascular amputees using these methods and achieved a 96% follow-up rate over a 12-month period among this elderly population with several comorbidities (not including mortality). The ESAA population is a healthier group. Our process of education, communication, and monitoring is as rigorous as that required by FDA trials and hence we are confident in our estimated follow-up rates.

All subjects must fulfill the following inclusion criteria:

- 1) Diagnosis of ankle arthritis, and decision in consultation with a surgeon to have ankle fusion or ankle replacement on one or both ankles to treat ankle arthritis. Patients will be clinical candidates for both surgical procedures.
- 2) Adult patients between 21 and 89 years of age.
- 3) Ambulatory (does not usually require a wheelchair) but whose primary impediment to pain-free ambulation is ankle arthritis.
- 4) Telephone number and stable mailing address so that he/she can be contacted throughout the course of the study.

Exclusion criteria include:

- 1) Recent surgical, neurological, metabolic, or lower limb musculoskeletal problem that might impair the ambulation measures in the study such as severe knee or hip OA.
- 2) Planned complicated foot and ankle procedure requiring multiple corrections.
- 3) Inflammatory arthritis with multi-focal disease (i.e., arthritis that affects multiple parts of the body).
- 4) Inadequate cognitive or language function to consent to participate.
- 5) Unable or unwilling to participate in clinic follow-ups and/or remote follow-ups for 24 months after surgery.
- 6) Unwilling or unable to comply with postoperative management program.

Under certain circumstances, an investigator may grant a waiver to enroll a subject who does not clearly meet all inclusion/exclusion criteria. This situation should seldom occur, but if it does, any deviations from the eligibility criteria must be documented on the screening CRF. Examples of acceptable deviations include:

- A subject states he/she does not have a permanent mailing address but can receive mail at a friend's house throughout the study.
- A subject will undergo a planned complicated foot and ankle procedure requiring multiple corrections; the investigator could potentially enroll the subject if baseline data could be collected before the first surgery and follow-ups could be scheduled after the main surgery (e.g., a staged total ankle replacement).

In order to add to the statistical power of the study, the de-identified data from a group of subjects who participated in a pilot study examining surgical treatment outcomes of ankle arthroplasty and arthrodesis,

will be added to this study via the Coordinating Center's De-identified Data Repository (MIRB # 00493, PI: Klute). These subjects met very similar inclusion/exclusion criteria and completed several of the same measures. A copy of the de-identified data collected from up to 358 subjects will be added to this study and included in several different analyses. This will be completed at the VA Puget Sound via a modification and waiver of consent/HIPAA authorization.

Assessments and Timeline

Surgical approach

The following arthroplasty and arthrodesis approaches, devices, and postoperative rehabilitation protocols will be used consistent with the standard of care provided by each of the participating institutions. In general, all surgeons will continue to use standard surgical protocols. All participating surgeons have at least 5 years of experience and have performed at least 30 arthroplasty and 30 arthrodesis procedures. Arthrodesis and arthroplasty are two current standard of practice procedures used to treat patients with ESAA; they are not investigational interventions.

Arthroplasty: Protocols are similar among participating centers, though implants are evolving. Each surgeon uses the recommended and clinically appropriate surgical approach, splints the ankles for 2-3 weeks, and restricts weight bearing for the first 3-6 weeks. Radiographs are performed at 6 weeks to determine weight bearing status. The study will involve only FDA approved implants with which the surgeon has established experience.

Arthrodesis: All surgeons will employ a well-established technique of rigid internal fixation. In this technique, the joint is prepared by removing cartilage from the surfaces, the bones are positioned as desired, and screws and/or a plate are attached to compress the bones together and prevent motion. This technique obviates the need for a cast or external support. Patients are allowed to walk with weight bearing aids immediately. Radiographs are performed at 6 weeks to determine weight bearing status. Weight is allowed on the limb in increments over the 3 to 12 weeks after surgery.

Questionnaires

To achieve our Primary Specific Aims, data will be collected on formal CRFs before surgery, and at 3, 6, 12 and 24 months after surgery; additional data may be collected annually on CRFs for up to 20 years post-surgery. The CRFs will record general demographic information (ethnicity, race, marital status, education level, employment status, socioeconomic status) and will assess subjects' overall physical function and ankle specific function; ankle pain intensity, duration of pain, and interference with activities; and general health. We will measure ankle specific function using the Foot and Ankle Ability Measure (FAAM). The FAAM measures several functional categories, is easily scored, and has been validated against the SF-36 physical function subscale. We will assess subjects' pain using four questions from the Chronic Pain Grade (CPG), which asks subjects to report the intensity and interference of their foot and ankle pain. The CPG has a simple and brief format, and it demonstrates good internal consistency and reliability. We will measure overall pain using the Bodily Pain subscore of the SF-36; we will measure subjects' general health using the SF-36 General Health subscore; and we will measure co-morbidities with the Functional Comorbidity Index (FCI) and a consumption history questionnaire (cigarettes and alcohol). Finally, we will ask subjects three questions at 3, 6, 12, and 24 months after their surgery to assess patient satisfaction with surgery and the role they played in the surgical decision-making process; additional satisfaction data may be collected annually for up to 20 years post surgery.

StepWatch™ Activity Monitor (SAM)

We will also ask subjects to wear a SAM (Orthocare Innovations, LLC) around their ankle for 7-14 days at each of four time periods: before surgery, and at 6, 12, and 24 months after surgery. The SAM provides

an objective measure of subjects' activity levels by monitoring the number of steps each day and step intensity (low, medium, or high speed). We will also ask subjects to fill out an activity log at the end of each day that the SAM is worn to provide insight about times of increased or decreased step activity. We will only ask subjects for a brief description of their activities (e.g., "I drove to work," "I went for a walk"), so the log should take about 5 minutes to complete each day. We will provide subjects with written instructions about wearing the SAM and keeping the log. In addition to the written instructions, study coordinators will instruct subjects how to use the SAM and to continue with normal daily activities while wearing the monitor.

Participants can be enrolled anytime preoperatively up until the day of surgery. Participants will ideally be enrolled at least 7-14 days before surgery to ensure enough time to wear the SAM. Subjects who are enrolled less than 7 days before surgery will not be asked to wear the SAM.

X-rays

The majority of subjects will have lateral and anterior-posterior weight bearing X-rays taken of their ankle throughout the course of their clinical care. Pre-surgical X-rays will be important to determine the baseline degree and severity of ESAA (see *Prognostic Factors*) to ensure that we can control for any imbalances between treatment groups; therefore, these will be required and will be collected as part of the research on our data collection forms. Subjects who do not undergo these standard X-rays as a part of their follow-up (i.e., post-operative) clinical care, will not be asked to have an X-ray for research purposes (i.e., follow-up appointments); however, should they occur, they will be documented as a part of routine clinical care.

Prognostic Factors

The following prognostic factors will be collected from the medical record (including X-rays/CT scans) sometime prior to or immediately after surgery: **demographic factors** (i.e., age, height, weight); **ankle factors** (i.e., cause of ESAA, degree of OA, previous ankle surgeries, varus/valgus alignment, degrees of subluxation, and severity of OA using the Kellgren-Lawrence Grading Scale¹⁴); **surgical factors** (i.e., surgeon, surgery type, surgery side, prosthesis brand and size, estimated blood loss, operating time, ancillary procedures, and any AEs during hospital stay); **general health** (i.e., medical history, comorbidities using the FCI through patient interview, BMI). Demographic factors will be obtained from the medical record and/or patient interview. The standard of care at each participating site varies. Items not documented in the medical record will be obtained through patient interview. Surgical factors will be obtained from the medical record and operative reports. Operating time is defined as procedure start to procedure stop. Estimated blood loss will be recorded based on a parameter of less than/greater than 300mL. Identifying prognostic factors that may be associated with the outcomes of interest is important to both identify potential subsets of patients who may be better candidates for one treatment over another and to control for potential confounding factors when comparing the two groups among all subjects if important baseline differences exist. The medical record will also be reviewed post-operatively at 1, 2, 3, 6, 12, and 24 months; it may also be reviewed annually for up to 20 years post-surgery. The purpose of the review is to track and record any expected or unexpected AEs, UAs, and SAs. All adverse events will be reported to the NIAMS and to the IRB according to the reporting guidelines at all of the participating sites.

Initial and Follow-Up Visits and Assessments

After the informed consent process, subjects will receive directions for wearing the SAM, an instruction sheet, and an activity log from a study coordinator. Subjects participating in the study at the VAPSHCS or Harborview Medical Center will receive the SAM materials in person or by mail. The VAPSHCS, which functions as the Coordinating Center, will mail SAMs and materials to participants using a secure, traceable shipping service. All SAMs and related materials will be returned from subjects to the

Coordinating Center using a prepaid trackable envelope. Monitors and questionnaires exchanged between the study coordinator and the patient are coded with a unique study ID. These materials do not contain the name of the subject or any other element of protected health information or personally identifiable information. Subjects who do not have enough time to wear the SAM for at least 7 days before surgery will be invited to participate in all other aspects of the study.

We will take a four-step approach to collecting questionnaire data on CRFs to achieve our Primary Specific Aims. (1) Study coordinators will conduct the baseline interview with subjects during a scheduled clinic appointment before surgery. (2) For subjects who are unwilling or unable to complete the interview during the clinic appointment, study coordinators will arrange a time to complete the interview with the patient by phone. (3) Alternatively, participants may elect to fill out the CRF during a clinic visit and a study coordinator will immediately check each page of the CRF for completeness. (4) Patients who are unwilling or unable to complete the interview in person or by phone will have the opportunity to take the CRF home or have it mailed to them and mail it back to the study coordinator. Study coordinators will call the participant within 5 days if they have not received the data. After receiving the data, study coordinators at participating sites will check the CRF for completeness and call the patient to obtain any missing or questionable data.

Patients will return for standard clinical appointments at the participating sites. Subjects will be followed immediately after surgery through at least 24 months and potentially up to 20 years after surgery. This will include time while hospitalized, routine standard of care visits, other planned visits at 3, 6, 12, and 24 months after surgery, and any unplanned visits. Subjects will receive a SAM to wear for 2 weeks at 6, 12, and 24 months after surgery. Other subject data will be collected on CRFs at 3, 6, 12, and 24 months after surgery, and, potentially, annually once per year for up to 20 years after surgery. Similar to the baseline interview, study coordinators will take a four-step approach to completing follow-up assessments. Table 2 summarizes the preoperative and follow-up study visits.

Notes to File

Sites will use a Note to File template to explain any clinic practices that are specific to a study site, document any discrepancies in regulatory documents, consent forms, or Case Report Forms, and to clarify any documents that are not complete or maintained as listed in the MOOP.

Table 2: Outcome measurements, methods, and timing of collection.

Type	Outcome	Measurement	Collected (Months)					Every 12 mo. up to 20yrs post-op
			0	3	6	1 2	2 4	
<i>Patient reported</i>	FAAM	Questionnaire	X	X	X	X	X	X
	SF-36	Questionnaire	X	X	X	X	X	X
	CPG	Questionnaire	X	X	X	X	X	X
	Patient satisfaction	Questionnaire		X	X	X	X	X
	Co-morbidities	Questionnaire	X			X	X	X
	Consumption	Questionnaire	X			X	X	X
	history	Questionnaire						X
	PLTOP(Seattle only)							
<i>Subject activity</i>	Step counts	Step activity monitors	X		X	X	X	
<i>Physiologic</i>	Complications*	Medical record		X	X	X	X	X
	ESAA factors	X-rays	X					

*Complications will also be recorded through medical record review at 1 and 2 months post-operatively.

Statistical Plan

Data analysis

The study is divided into primary and secondary specific aims. Both aims are included in the data analysis plan. Power calculations are based on the primary specific aims.

Descriptive statistics

For categorical variables, proportions and frequency counts will be calculated. For continuous variables, means and standard deviations will be computed. Additionally, minimum, maximum, and range will be reported for both categorical and continuous variables. Furthermore, the distribution of missing data, particularly in the outcome variables, will be explored with attention to potential biases in our results produced by the pattern of missingness over the follow-up. Group comparisons of categorical variables will be made using Pearson's Chi-Square (χ^2) tests and continuous variables using t-tests.

Primary specific aims

Cross-tabulations will be performed on all potential confounding factors to assess their association with each surgical group and each outcome of interest to identify key variables necessary for inclusion in our regression models evaluating our primary aims. Linear mixed effects models will be used to compare mean scores (overall, subscale, and change) from the 12-month, 24-month, and any additional annual assessments, FAAM, CPG, and SF-36 scales between patients undergoing ankle arthrodesis and ankle arthroplasty. The basic form of the model is:

$$Y = \beta_{01} + \beta_1 S + \beta_2 T + \beta_3 ST + \beta_4 W_1 + \dots b_0 + b_1$$

Y = outcome (FAAM, CPG, or SF-36 score)

T = follow-up time (baseline, 3, 6, 12, 24 months, etc.)

S = surgery type (arthrodesis or arthroplasty)

W_1 = other confounders or covariates, including surgery assignment (arthrodesis vs. arthroplasty)

The β s are fixed effects coefficients estimated by the model. The main coefficient of interest is β_3 , the significance of which implies that the pattern of change in outcome across time differs by surgery. If this interaction is not significant, then there would be no evidence that the outcome is affected by surgery type. The other components of this model are the random effect terms, denoted by b . The first term, b_0 , is the random effect due to study site, and b_1 is the random effect due to participant within site. Other random effects terms may be added to account for the variability in the relationship between surgery and outcome by study site, and the variability in the change in outcome over time across participant. Other fixed effect terms can be added to determine if other variables (in particular, study preference) modify the relationship between the improvement in outcome over time by surgery type by using a 3-way interaction term: $S*T*W$.

The basic model described above assumes a linear improvement in outcome over time. This time could also be modeled as polynomial (replacing T in the basic model with $T + T_2 + \dots$), or as a categorical variable with baseline time as the reference category and separate indicator variables representing time at 3 months, 6 months, etc. In the categorical scenario, $T_3 + T_6 + \dots T_{24}$ would be substituted for T ; where T_i represents the outcome difference between the i^{th} month of follow-up and baseline. This latter parameterization allows us to examine individual differences in outcome at each follow-up, as well as follow-up differences together.

Secondary specific aims

Secondary Aim 1: To identify intrinsic and extrinsic prognostic factors which are predictive of higher FAAM scores, CPG, SF-36 scores, overall patient satisfaction, and step counts, we will first estimate the association between each prognostic factor and potential confounding factor and each outcome (bivariate analysis) at measured intervals and final follow-up. The initial model will include all candidate predictors and potential confounding factors. Independent predictors of outcome will be identified by forward stepwise logistic regression where all univariate predictors with a p-value ≤ 0.05 will be included. Final models will be determined by prognostic factors and potential confounding factors that account for the majority of the variance (R2 value). Statistical assumptions will be verified graphically. Models will be examined to determine if multicollinearity is present using condition number and variance inflation factors. Furthermore, outliers and influential values are identified using studentized residuals and Cook distances. A modified bootstrap approach (random sampling with replacement) will be used to obtain several internal validation samples. The overall prediction model will be applied to these samples and a coefficient of determination (R2) will be calculated as an indicator of the performance of the proposed prediction model.

Secondary Aim 2a: Logistic regression (with mixed effects modeling) will be used to compare the presence of post-surgical complication rates at 3, 6, 12, 24 months, and any additional annual periods assessed, between patients undergoing ankle arthrodesis and ankle arthroplasty to control for other potential predictors of outcome and to account for random variability due to differences in complication rates by site. Odds ratios and 95% confidence intervals will be calculated. All follow-ups will be examined, although the majority of complications will likely occur in the first 6-12 months.

Secondary Aim 2b: Linear mixed effects models (as described in the primary aims section) will be used to compare step counts pre-operatively, and at 6, 12, and 24 months post-operatively between subjects undergoing ankle arthrodesis and ankle arthroplasty.

Secondary Aim 2c: A binary outcome, rather than a continuous outcome, will be used to compare rates of patient satisfaction at 12 and 24 months, and any additional annual periods assessed, between patients undergoing arthrodesis and arthroplasty. The model will be similar to that described in the primary aims

section. The model will be a logistic mixed effects model to account for variability in patient satisfaction due to site, and within patient variability across follow-up time.

Data review and analysis with respect to the primary and secondary aims will not occur until all subject follow-up for a given time point is complete unless an interim analysis is requested by the DSMB or Safety Monitor. The review of safety data may result in the steering committee deciding to temporarily halt enrollment and contact the DSMB chair or Safety Monitor for an interim DSMB or Safety Monitor review to determine if the study needs urgent modification or stopping. Should the protocol or data collection plans or study forms be amended as a result of data review, the participating IRBs will be notified and the amendment approved prior to implementation of the study amendment. In addition, subjects will be notified of any significant new findings that develop during the course of the research that may affect their willingness to continue participating in the study.

Subject and Study Termination

The reasons for terminating a subject from the study include (but are not limited to):

- Death
- Concurrent illness directly preventing further participation
- Voluntarily withdrawal of consent
- Investigator-requested withdrawal for safety reasons (e.g. AE)
- Lost to follow-up. Every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. The measures taken to ensure follow-up must be documented

Ongoing Adverse Events (AE) Review

Note: As the study funds are nearly exhausted, surgical and other health related SAE/AE reporting practices involving the Safety Officer, will be suspended after all subjects have completed the 24-month follow-up and the final Safety report has been submitted (anticipated completion in Spring 2018). Collection of this SAE/AE data for study purposes will continue. Reporting of research related SAEs/AEs/Other Problems will continue per each active site's local IRB requirements, however to minimize administrative burden, SAEs/AEs that are not related to the research procedures will no longer be summarized and reported with continuing review; the ankle surgery was standard care, not a research procedure.

Unscheduled visits can take place at any time during the study in case of patient request, medical emergencies or if the physician considers this to be appropriate for patient care. At each unscheduled or planned visit, the investigator will check for the presence of any AEs or complications as per normal standard of care.

Study coordinators will record these AEs on the post-operative factors section of the CRFs. This section tracks expected AEs, as well as unexpected AEs and SAEs. Study coordinators are prompted to fill out an Adverse Event Log describing the details, severity, and outcomes of AEs and a separate CRF for SAEs. At a minimum, information recorded on the AE log form and SAE CRF includes the subject ID, event description, event start and stop dates, event severity, relatedness, event treatment/action, event outcome to date, and expectedness. Each event will be evaluated to determine if there is any reason to modify a patient's management plan or withdraw them from the study (see previous section). Additionally, the study coordinator will screen the medical record post-operatively at 1, 2, 3, 6, 12, and 24 months, and,

potentially, annually for up to 20 years. If applicable, additional surgeries, new AEs, and new SAEs are recorded on the post-operative factors of the CRF.

Subjects are electing to undergo surgery regardless of whether or not they choose to participate in this study. Expected AEs are those that might reasonably be expected to occur in this population after ankle surgery. These events include the following: immediate post-operative pain, complications from anesthesia, superficial wound infections, osteomyelitis and deep infection, intraoperative fracture, nonunion or malunion, malalignment, arthritis in adjacent joints, leg length discrepancy, wound dehiscence or skin slough, reflex sympathetic dystrophy, implant failure, implant migration or subsidence, irritation from ectopic bone around hardware, refracture, superficial peroneal neuropraxia, tarsal tunnel syndrome, amputation, chronic edema, chronic ankle pain, stress fractures, osteolysis, and implant loosening. Expected AEs will be recorded on the CRFs for analysis purposes since we are comparing the safety of both interventions. Site Principal Investigators and study coordinators may also use the "other" category on this section of the CRF to designate other expected events based on the subject's medical history and comorbidities. In addition to recording AEs on CRFs, site study coordinators will also use an Adverse Event Log Form (Appendix D) to document all AEs. Sites will send copies of these logs to the data manager at Spectrum Research for data entry. Sites will also maintain a master adverse event log form electronically in Excel. Sites will send the master log form to the Coordinating Center and Spectrum Research biannually so that the data can be compiled and reviewed by the Safety Officer (the DSMB was disbanded effective 11-04-2016); Safety Officer review will continue only through the end of the 24-month data collection for all subjects. All AEs will be reported to the IRB according to guidelines at all of the participating sites. Sections 3.n.2-4 provide more details on AE and UAE/SAE reporting.

The PI at each site will indicate whether or not the AE is serious and related to study participation on all reports submitted to the IRB and NIAMS.. Sites will adhere to institutional requirements for determining severity and relatedness of AEs. Sites will also follow individual IRB reporting requirements for all AEs.

Data Management

Once completed and reviewed by site study coordinators, copies of the CRFs will be sent to VAPSHCS using a secure traceable mailing service. The CRFs do not contain identifiable information and only the study ID. Data from the CRFs will then be checked by the data manager at Spectrum Research. After a thorough review and query of the CRFs (see process below), the VAPSHC study coordinator will enter the data into a secure, password protected database via OpenClinica®. OpenClinica® will be used for the front end which will be linked to a secure SQL-based database. The data cells of the database will mirror the data cells from each CRF. Data entry will be validated (i.e. logic checks including range checks, missing value checks, etc.) both by visual inspection and built-in programming logic during the data entry process. Follow-up will be considered complete once the patient's follow-up time is accounted for as being censored or they have completed their final follow-up. The study database will act as a repository for all collected data and will be inaccessible by anyone without pre-assigned confidential password access. An aggressive database backup schedule will be implemented and closely administered. This database backup schedule is implemented in two parts; information that has been entered via OpenClinica® will automatically backup on a daily basis on the webserver, and the information will undergo routine manual backup in Spectrum Research's own physical database.

To ensure the security of data entered, the data entry website will be hosted through a well-known webhost, www.networksolutions.com. The data encryption method (256 Bit SSL) meets VA standards. This ensures secure data transfer from webhost to webserver.

To ensure the accuracy of the data, the following processes will be implemented:

1. All forms will be checked for completeness and appropriateness by the VAPSHCS study coordinator. Discrepancies will go through a formal query process described below. The CRFs will not contain any confidential or identifiable patient information.
2. All data collection forms will be inventoried, indicated by date received, form received, and who received; and re-checked for completeness by the data manager.
3. Once the data inventory has taken place, the data will be placed into a data entry queue for double-checking by another member of the research team.
4. Range limits and parameters will be included to reduce the potential of incomplete data and inaccurate data.

Once data are entered, periodic data queries of the database will be run by the data manager to look for any discrepancies or inaccuracies in the data (e.g., missing and nonsensical values) that may have not been picked up during the CRF screening process. After initial CRF screening or database querying, any discrepancies or inaccuracies will be communicated electronically to the appropriate site study coordinator using a Data Clarification Form (DCF; figure 4). The site study coordinator will reconcile the query by contacting the patient, the PI, or accessing the source data which may include the medical record. No changes to the original CRF will be made. The coordinator will correct the error or complete the missing value (if possible) in the DCF and send back to the data manager who will correct the database. The DCF will be stapled to the original CRF so that there is a paper trail of all CRF queries and database changes.

3.B SCHEDULE OF VISITS AND EVALUATIONS

Orthopaedic surgeons, who are study investigators, will inform potentially eligible subjects that they may be eligible to participate in a research study for patients undergoing surgical correction for ESAA. Interested patients will then speak to a study coordinator during their clinic visit. If someone from the research staff is unavailable during the clinic visit, then the subject will be mailed an approach letter to determine interest in the study. Study coordinators will arrange a time to meet with eligible subjects to complete the informed consent and HIPAA authorization form. This meeting will take place before or after an orthopaedic clinic appointment or at another time that is convenient to the subject. Sites will follow IRB-approved methods for obtaining informed consent and HIPAA authorization.

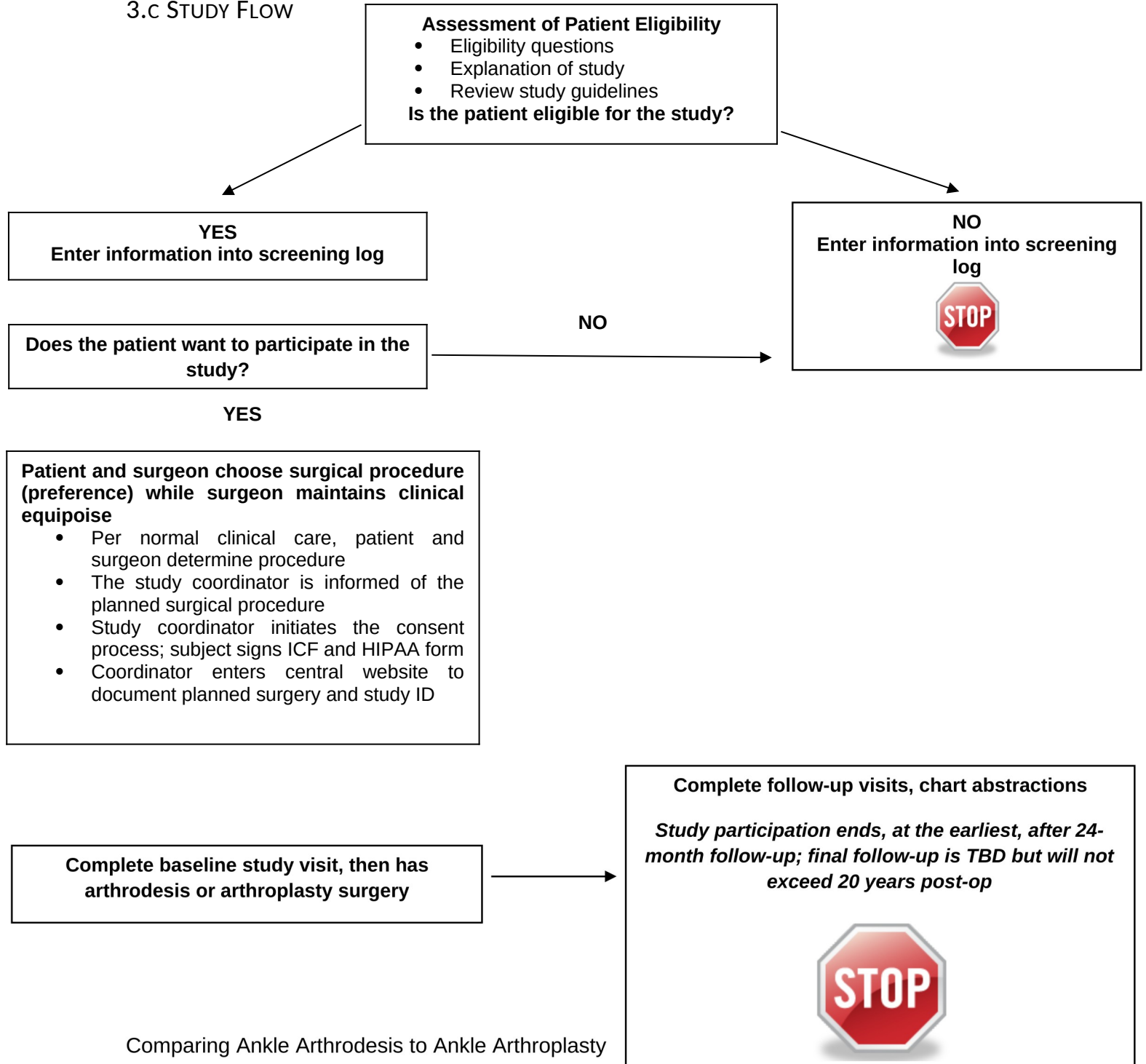
To achieve the specific Primary Aims of the study, subjects are assessed before their ankle surgery and at 3, 6, 12, and 24 months and, potentially, thereafter every 12 months for up to 20 years after surgery using formal CRFs. For our secondary aims, subjects will also be asked to wear a SAM around their ankle to monitor their daily activity. Subjects wear the SAM for 7-14 days at four time periods throughout the study (before surgery and at 6, 12, and 24 months after surgery). While wearing the SAM, subjects also fill out a simple log of daily activities.

Subjects are not required to schedule separate clinic visits. Subjects are typically evaluated clinically before surgery and at post-operative intervals that align with the study follow-up periods. The study coordinator will meet with subjects before or after their clinic appointment to complete the interview and exchange study materials. Subjects at participating sites except VAPSHCS and Harborview Medical Center will complete the interview with a site study coordinator but will be mailed a SAM, instruction sheet, and activity log. All subjects receive a postage-paid trackable envelope to return the study materials. We will make every attempt to complete interviews in person or by phone; if a subject is unwilling or unable to complete the interview in person or by phone, study coordinators will ask the patient to fill the CRF out at a clinic visit or fill it out at home and return it by mail (this method is described in

greater detail in Scope 3.L.2.). Figure 2 illustrates the schedule of study visits; the visits align with routine clinical care visits, or, subjects will receive the study materials via mail from a study coordinator. All initial and follow-up procedures will occur according to the following schedule:

- Baseline: anytime preoperatively, up to the day of surgery
- 3 month ± 1 month
- 6 month ± 1 month
- 12 month ± 2 months
- 24 month ± 4 months
- Every additional 12 months ± 4months, for up to 20 years post-op

3.C STUDY FLOW



3.D STUDY ORGANIZATION AND RESPONSIBILITIES

This is a large multi-site study with six participating institutions. The VAPSHCS in Seattle, WA serves as the Coordinating Center.

3.D.1 ROSTER

Study Staff at Coordinating Center

VA Center for Limb Loss Prevention and Prosthetic Engineering

VA Puget Sound Health Care System (Seattle, WA)

Role	Name & Title	Contact information
PI	<p>Bruce J. Sangeorzan, MD</p> <p>Director, VA Center for Limb Loss and Mobility</p> <p>Chief of Orthopaedics, Harborview Medical Center</p>	<p>VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108</p> <p>Office: (206) 277-3223 Fax: (206) 277-4285 Bruce.Sangeorzan@va.gov bsangeor@u.washington.edu</p>
Co-Investigator	<p>William R. Ledoux, PhD</p> <p>Research Biomedical Engineer, VA Center for Limb Loss and Mobility</p>	<p>VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108</p> <p>Office: (206) 768-5347 Fax: (206) 277-4285 William.Ledoux@va.gov wyledoux@u.washington.edu</p>
Clinical Trial Consultant/Epidemiologist	<p>Daniel C. Norvell, PhD Clinical Epidemiologist</p> <p>Vice President, Spectrum Research, Inc.</p>	<p>Spectrum Research, Inc. 705 S 9th Street, Suite 203 Tacoma, WA 98403</p> <p>Office: (253) 722-2210 Mobile: (253) 906-5308 Fax: (253) 722-2810 dan@specri.com</p>
Data Manager	<p>Ian Ellis, BS</p> <p>Data Manager & IT Specialist, Spectrum Research, Inc.</p>	<p>Spectrum Research, Inc. 705 S 9th Street, Suite 203 Tacoma, WA 98403</p> <p>Office: (253) 722-1900 Fax: 253-722-2810 ian@specri.com</p>
Statistician	<p>Jane B. Shofer, MS</p> <p>Statistician, VA Center for Limb Loss and Mobility</p>	<p>VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108</p>

		shofer@u.washington.edu
Project Manager The Clinical Trial Consultant, Program Coordinator and Study Assistant/Coordinator will take over the responsibilities of this role for the time being.	Sienna Williams, BA Research Project Manager	VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108 Office: (206) 277-1505 Fax: (206) 277-4285 sienna.williams@va.gov
Study Assistant/Coordinator	Ngaio, Lace, BS Research Coordinator, VA Center for Limb Loss and Mobility	VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108 Office: 206-764-2962 Fax: (206) 277-4285 Jennifer.Hicks4@va.gov

Study Staff at Harborview Medical Center (Seattle, WA)

Role	Name & Title	Contact information
Site PI	Bruce J. Sangeorzan, MD Director, VA Center for Limb Loss and Mobility Chief of Orthopaedics, Harborview Medical Center	VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108 Office: (206) 277-3223 Fax: (206) 277-4285 Bruce.Sangeorzan@va.gov bsangeor@u.washington.edu
Co-PI	William R. Ledoux, PhD Research Biomedical Engineer, VA Center for Limb Loss and Mobility	VA Puget Sound Health Care System RR&D, MS-151 1660 S. Columbian Way, Seattle WA 98108 Office: (206) 768-5347 Fax: (206) 277-4285 William.Ledoux@va.gov wrledoux@u.washington.edu
Co-Investigator	Michael E. Brage, MD Associate Professor and Attending Surgeon, Orthopaedics and Sports Medicine University of Washington Harborview Medical Center	Harborview Medical Center Box 359798 325 9 th Ave Seattle, WA 98104 Office: (206) 744-3466 Fax: (206) 744-3227 bragem@u.washington.edu
Site Coordinator	Julie Agel University of Washington Harborview Medical Center	bagel@uw.edu

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Study Staff at Orthopaedic Associates of Michigan, PC (Grand Rapids, MI)

Role	Name & Title	Contact information
Site Co-Investigator	Donald Bohay, MD Orthopaedic Surgeon	Orthopaedic Associates of Michigan, PC 1111 Leffingwell Grand Rapids, MI 49525-6406 Office: (616) 459-7101 donald.bohay@oamichigan.com
Study Coordinator	Michelle A. Padley, BS, CRMT Director of Research/Fellowship Manager	Orthopaedic Associates of Michigan, PC 1111 Leffingwell Grand Rapids, MI 49525-6406 Office: (616) 459-7101 x1797 Fax: (269) 459-9693 Michelle.Padley@oamichigan.com
Research Regulatory Specialist	Lindsey A. Behrend, BS Research Regulatory Specialist	Orthopaedic Associates of Michigan, PC 1111 Leffingwell Grand Rapids, MI 49525-6406 Office: (616) 459-7101 x1358 Fax: (269) 459-9693 Lindsey.Behrend@oamichigan.com

Study Staff at Orthopedic + Fracture Specialists (Portland, OR)

Role	Name & Title	Contact information
Site PI	James Davitt, MD Orthopaedic Surgeon	11782 SW Barnes Road Suite 300 Portland, OR 97225-5933 Office: (503) 214-5259 jamesdavitt@yahoo.com james.davitt@providence.org
Study Coordinator	Jacqueline Shelton, BS, CCRP Research Assistant	11782 SW Barnes Road Suite 300 Portland, OR 97225-5933 Office: (503) 608-5177 jacqueline.shelton@oandfs.com

Study Staff at Minnesota Orthopedic Sports Medicine Institute at Twin Cities Orthopedics (Edina, MN)

Role	Name & Title	Contact information
Site PI	J. Christiaan Coetzee, MB, ChB	Minnesota Orthopedic Sports Medicine Institute at Twin Cities Orthopedics

	Orthopaedic Surgeon	4010 West 65 th Street Edina, MN 55435-1706 Office: (952) 456-7136 jcc@tcomn.com
Study Coordinator	Becky Stone, MS, ATC Research and Education Supervisor	Minnesota Orthopedic Sports Medicine Institute at Twin Cities Orthopedics 4010 West 65 th Street Edina, MN 55435-1706 Office: (952) 456-7136 Fax: (952) 944-0460 beckystone@tcomn.com

3.D.2 COORDINATING CENTER

The VA RR&D Center at the VAPSHCS (Seattle, WA) is the Coordinating Center for this multi-site project. The PI (Bruce J. Sangeorzan, MD), the Project Manager and/or other designated staff, and Clinical Trial Consultant/Epidemiologist (Daniel C. Norvell, PhD) will be responsible for all pre-study tasks and training. These tasks include assistance and oversight with IRB submissions at each site, traveling and training study coordinators and investigators at each site, development of the CRFs, database development, and development and maintenance of the study SOPs and MOOP. Additionally, the Coordinating Center is responsible for the following items:

- 1) Communication with sites: The Coordinating Center is responsible for routine communication with all of the participating sites. During the pre-study phase, the Coordinating Center will hold bi-weekly conference calls with sites and visit each site for training and assistance with the IRB application and related materials. Once recruitment begins, the PI and/or PM/other designated staff will hold monthly conference calls with site investigators and/or study coordinators to discuss recruitment, enrollment, and overall study progress. Staff members at the Coordinating Center are also available directly by phone and e-mail.
- 2) Preparation and submission of reports: The data manager, project manager/designated staff, and biostatistician (as requested) are responsible for preparing monthly progress reports for multisite conference calls and also prepare bi-annual reports for the Safety Officer (DSMB prior to 11-04-2016), NIH, and NIAMS for review through the end of the 24-month data collection. The project manager also is responsible for submitting monthly enrollment reports to NIAMS (enrollment was completed April 30th 2015). The PM/designated staff will communicate regularly with the individual sites to receive the information on recruitment, enrollment, eligibility, follow-up rates/attrition, and AEs to prepare these reports. Sites will maintain and update screening logs, enrollment logs, retention logs, and AE logs (as noted above).
- 3) Distributing changes to the study protocol, SOPs, or MOOP to all sites: The PI and PM/designated staff, are responsible for ensuring timely changes to the study protocol, SOPs, or MOOP. The PM is responsible for maintaining all regulatory documents, including the study protocol, MOOP, and other SOPs. The PM/other designated staff and IRB program coordinator at the Coordinating Center are responsible for all IRB submissions. The PM will update all sites of these changes. It is the responsibility of the site study coordinator to submit the modified documents to the local IRB for approval. The Coordinating Center will also communicate a timeline for submitting changes to the

local IRB (e.g. “this protocol change must be submitted within 5 business days of receipt of the email”).

- 4) IRB assistance and oversight: The PM and additional study staff from the Coordinating Center will oversee individual site IRB application procedures and any modifications, continuing review reports, and AE reports throughout the course of the study. Site study coordinators will be responsible for preparing and submitting these forms, but staff at the Coordinating Center will be available for questions and assistance. The Coordinating Center will also maintain a record of IRB approval letters from participating sites. The PM and other staff at the Coordinating Center are responsible for timely submission of all Safety Reports. Safety Reports will be submitted to the study sites and to the VAPSHCS IRB within 5 business days of receiving the report. Study sites will follow local IRB guidelines for submitting Safety Reports to the IRB.
- 5) AE monitoring and reporting: Participating sites are responsible for notifying the PM/designated staff and PI at the Coordinating Center of any UAEs/SAEs in a timely manner of learning about the event. The event is also reported to the site investigator and study coordinator; each site will follow its individual IRB reporting requirements for AEs. The Coordinating Center is responsible for reporting SAEs to the Safety Officer/NIAMS every six months (through the end of the 24-month follow-up), and also for maintaining a log of all AEs, UAEs, and SAEs. The Coordinating Center also maintains an AE log, tracks and reports all AEs, and prepares bi-annual AE reports for the Safety Officer (through the end of the 24-month follow-up). See study protocol and section 3.n.2-4 for additional details.
- 6) Data oversight: The Coordinating Center will have regular contact with the study staff at other sites and the data management team to ensure the data is of the highest quality and integrity. The PM/designated staff will ensure that the data management and query SOPs are being followed. A more detailed description of this process can be found in section 3.r. (Data Flow)
- 7) Site visits: **The NIAMS has determined these monitoring activities are no longer required.** A study monitor from the Institute of Translational Health Sciences (ITHS), which is part of the University of Washington, will periodically visit each site to ensure that the protocol is being followed, informed consents and HIPAA authorization forms are being signed and dated appropriately, and to verify the study CRFs match the source documents for all inclusion/exclusion criteria and primary aims data. During the site visit, additional or refresher training may also take place. The goal of the site visits is to maximize recruitment, achieve complete accountability of all patients enrolled, ensure the protection of patient rights, and ensure data integrity. The PI and PM at the Coordinating Center are responsible for reviewing the monitoring reports from the ITHS monitors and for submitting them to KAI, NIAMS, and Safety Officer for their review. See section 3.v.4. for additional details, including the specific monitoring plan.

3.D.3 CLINICAL SITES

Investigators and study staff members at the participating sites are responsible for the following items:

- 1) Completing annual training: All study staff are responsible for completing the *CITI Human Subjects Protection & Good Clinical Practices* course in accordance with site institutional requirements. Study staff are also responsible for meeting local requirements for all research-related training programs. A copy of the completion certificate for the CITI course should be sent to the Coordinating Center.
- 2) IRB submissions: Study coordinators are responsible for preparing all initial, modification, and annual reports and submitting them to the IRB. Study coordinators will maintain regular contact with the site

PIs and the PM/designated staff at the Coordinating Center; the Coordinating Center will provide any necessary assistance with site IRB submissions. Copies of the initial and annual IRB approval letters from each site will be sent to the Coordinating Center.

- 3) Regulatory binder: Study coordinators are responsible for maintaining a site regulatory binder. At a minimum, the binder should include:
 - a. Registration Documents
 1. *Curriculum vitae* for Principle Investigator, Co-investigators, and Study Coordinator
 2. Required training certificates for all study personnel
 - b. Background Materials
 1. Study Brochure
 - c. Protocol and Modifications, study specific SOPs
 1. MOOP
 2. IRB Materials
 - i. IRB membership roster
 - ii. IRB approval of the protocol and consent
 - iii. IRB approval of advertisements and other recruiting materials, if applicable
 - iv. Correspondence between the Investigator and the IRB
 - v. Submission of Progress Reports to the IRB
 - vi. Submission of SAEs to the IRB
 - vii. Notification to the IRB concerning study termination
 - d. Informed Consent
 1. Blank copies of all versions of the consent and assent forms used in the study
 2. Signed consent forms
 - e. Forms and Logs
 1. Study Responsibilities Form
 2. Monitoring Log
 - f. Standard Agreements
 1. Confidentiality Agreement (may also be stored in the institution's contract department)
 - g. Correspondence
 - h. Case Report Forms
 1. Blank copies of original and any updated CRFs
 2. CRF guidelines
 - i. Communication log of all meetings (in-person and teleconference)

- 4) Individual binders will be maintained for the following purposes:
 - a. Communications binder
 1. Communication log of all meetings (in-person and teleconference)
 2. Telephone communications log of all important phone conversations with study personnel at other sites
 - b. Consent form binder
 1. Enrollment log
 2. Log of approved consent versions
 3. Signed consent forms
 - c. Education binder
 1. Initial study training documents
 2. Continuing education training documents (annual trainings)
 - d. CRF binder
 1. CRF guidelines
 2. Copies of all approved CRFs
 3. CRF changes log
- 5) Conducting the overall study: The site investigators are responsible for overseeing study operations and ensuring that study coordinators are conducting the study according to the protocol and the MOOP. Research team members at each site are responsible for adhering to the protocol and consulting with the site PI or staff at the Coordinating Center when necessary.
- 6) Subject identification, enrollment, and follow-up: Study coordinators at each site are responsible for identifying, recruiting, screening, enrolling, and retaining participants. They are also responsible for assigning a study ID number once a subject enrolls in the study.
- 7) Informed consent: Study coordinators, with the oversight of the site investigators, are responsible for going through the informed consent process with study participants. Study coordinators should ensure that all consent and HIPAA authorization forms are signed and dated appropriately and are stored in the secure location described in the protocol (see section 3.h.1-3). During the informed consent process and throughout the course of the study, study coordinators should also ensure that participants' rights are protected by adhering to good clinical practices and following the study protocol.
- 8) Collecting initial and follow-up study data: Study coordinators are responsible for interacting with study participants to ensure that subjects are correctly wearing the SAM. Study coordinators are also responsible for ensuring interviews are completed within the specified windows and that all data on the CRFs are accurate and complete. Study coordinators will interact with the data manager through an established data query process to ensure any missing or incomplete data is accounted for.
- 9) Preparing reports: Study coordinators at each site are responsible for preparing monthly reports (recruitment, enrollment, study progress) and sending them to the Coordinating Center for monthly conference call meetings. This information is submitted securely and electronically on the website developed by Spectrum Research, Inc.

- 10) Maintaining accurate study records: Study coordinators will maintain paper and electronic study records according to the study protocol. They are also responsible for preparing for site monitoring visits or audits of regulatory documents, informed consent forms, CRFs, and source documents.
- 11) Communicating with the Coordinating Center: Site investigators and study coordinators are responsible for routine (written and verbal) communication with the PM and PI at the Coordinating Center. In addition to monthly conference calls, study staff at each site will contact the Coordinating Center when learning about AEs, submitting IRB reports, learning about a change in contact information for a patient, questions or concerns about the protocol or MOOP, or any other issue related to the daily operations of the study.

3.D.4 PHARMACY ACTIVITIES (N/A)

3.D.5 STEERING COMMITTEES

The steering committee will include staff at the Coordinating Center (PI, PM/designated staff, co-investigator, statistician), the Clinical Trial Consultant/Epidemiologist, and site PIs from at least two of the participating sites. The NIAMS Program Official is also a member of the Steering Committee; this role will phase out as the remainder of the grant funds are spent. This committee will be responsible for the final “locked” protocol, final CRF package, and all the operational plans outlined in this MOOP. They will also be called on periodically during the course of the study to evaluate AEs, consider protocol modifications, meet with the Safety Officer (if needed), evaluate individual site progress, and other study related oversight.

3.D.6 EXECUTIVE COMMITTEES (N/A)

3.E TRAINING PLAN

General training: All study staff are responsible for completing the online course (*Human Subjects Protection and Good Clinical Practices*) on the CITI website every three years. Sites that have institutional requirements for completing CITI training may adhere to their institutional policy. Copies of the completion report for this training should be forwarded to the Coordinating Center and should be maintained at each site in a regulatory binder.

Site-specific training: All study staff at participating sites are responsible for meeting the annual requirements of their local institution. Copies of training certificates will be maintained locally.

Study-specific training: The PI will hold an initial and annual investigators meeting with all of the investigators and study coordinators to introduce the study protocol and procedures, and later, to discuss overall study progress. This meeting will occur during the AAOS or American Orthopaedic Foot and Ankle Society (AOFAS) annual meeting; after October 2017 the annual meeting may be conducted via conference call to minimize costs.

Site initiation visit: After the investigators meeting, the PI and PM or a representative from the Coordinating Center will travel to each site during the pre-study phase for pre-study planning, education, and training. During this training session, staff from the Coordinating Center will ensure that all study materials (e.g., protocol, MOOP, brochures, CRFs) are discussed and reviewed, that staff fully understand the study procedures and SOPs, and that all regulatory documents are approved and filed appropriately in a regulatory binder. There will be a review of the items from the investigators meeting to include the recruitment, informed consent, and randomization process for the study. Additional

conference calls with all study coordinators may be held prior to the start of the study if there are outstanding items not covered during the site visit.

At the conclusion of the visit, the Coordinating Center representative must be satisfied that all staff members participating in the study are sufficiently informed to competently fulfill their responsibilities. All unresolved issues should be discussed with the PM and then readdressed with the Principal Investigator.

A Study Initiation Visit will be conducted after a site has been selected to participate in a trial but before subject screening and enrollment begins. This visit allows *all* research personnel on this project to receive detailed instruction concerning their role in the study. This visit may take place in-person or may be an electronic visit with certain items discussed via teleconference.

The PI, monitor, and/or PM may travel annually to each site to provide any necessary refresher training and perform on-site audits of IRB protocols, regulatory documents, source documents, and electronic documents.

3.F COMMUNICATIONS PLAN

The PI will hold an annual meeting with all of the site investigators and study coordinators to ensure ongoing communication and adherence to the study protocol. Additionally, the PI, PM, site investigators, study coordinators, and any additional study staff who are able to attend will participate in monthly conference calls. The purpose of the monthly meetings is to discuss study progress, issues with recruitment/enrollment/retention, UAEs or SAEs and to share successful strategies.

The PI and PM/designated staff at the Coordinating Center are responsible for communication related to regulatory requirements, protocol deviations, adverse events and Safety Reports. Specific requirements are outlined in 3.O Data Safety Monitoring Activities and 3.P Study Compliance.

Communication with the Steering Committee is outlined in section 3.d.5 of the MOOP.

Communication with the Safety Officer, NIH, and NIAMS is outlined in the Data and Safety Monitoring Plan.

3.G RECRUITMENT, SCREENING, AND ELIGIBILITY CRITERIA

3.G.1 RECRUITMENT PLAN

Study coordinators will pre-screen weekly clinic lists of all upcoming appointments. Study coordinators will speak with investigators about potentially eligible subjects during clinic appointments. At the end of the clinical exam, surgeons will determine if the potential participant has a preferred treatment and then introduce the study to determine if they would like to speak to a study coordinator to receive more information (see section 3.i for details).

If the patient agrees, the study coordinator is provided with the name and contact information of the subject. The study coordinator screens the medical record to confirm the subject meets the inclusion/exclusion criteria for the study. If possible, the study coordinator will then speak to interested patients at their next clinic appointment to discuss participation. When unable to speak with patients at a clinic appointment, the study coordinator will send an approach letter which includes information about the study and a phone number to call if the patient prefers to opt-out of the study. The study coordinator will wait approximately 1 week to call patients to explain the study.

Additionally, IRB-approved fliers announcing the study will be posted in the clinic space at each of the participating sites. Pending IRB approval, information about the study will also be available electronically on **www.clinicaltrials.gov** and on the website of each of the clinic offices.

3.G.2 SCREENING

Upon patient agreement, eligibility will be verified using a screening CRF based on inclusion/exclusion criteria, and the study coordinator will initiate the informed consent process and determine the treatment group. Subjects will be screened using the medical record and a series of questions, administered over the phone or in person at a clinic visit.

Under certain circumstances, an investigator may grant a waiver to enroll a subject who does not clearly meet all inclusion/exclusion criteria. This situation should seldom occur, but if it does, any deviations from the eligibility criteria must be documented on the screening CRF. Examples of acceptable deviations include:

- A subject states he/she does not have a permanent mailing address but can receive mail at a friend's house throughout the study.
- A subject will undergo a planned complicated foot and ankle procedure requiring multiple corrections; the investigator could potentially enroll the subject if baseline data could be collected before the first surgery and follow-ups could be scheduled after the main surgery (e.g. a staged total ankle replacement).

3.G.3 SCREENING LOG

All subjects who complete the screening process will receive a screening number (e.g. S1001, S1002, S1003, etc.). A screening log will be maintained locally at each of the individual sites in a password-protected electronic file located on a secure server. The log will include the screening number, the subject's last name, first initial, and date of screening. The status of the screen (eligible or not eligible) and reason for screening failure or refusal to participate in the study will also be recorded. Identifiable information (last name and first initial) will be stored until the end of the recruitment period to ensure that subjects who are not eligible or not interested are not approached more than once about participating in the study.

In order to track overall screening for the study and produce enrollment progress reports, a master screening log will be maintained by Spectrum Research. The log is hosted electronically on a website, www.spectrumtrial.com. This website is linked to the OpenClinica® database. This file will not contain last names or first initials of the subject but will contain the screening number, date of screening, eligibility status, and reason for screen failure or refusal. Access to the master screening log is regulated by a secure login ID and password for each site.

3.G.4 ELIGIBILITY CRITERIA

See protocol section 3.a.

3.H INFORMED CONSENT AND HIPAA

3.H.1 INFORMED CONSENT PROCESS

Informed consent is a process that gives individuals the opportunity to decide whether they want to participate in a study. During this process, individuals should be informed of all aspects of the study that are relevant to their decision. The participants then confirm their willingness to participate in a particular research study by signing the Informed Consent Form (ICF).

Subjects must sign an ICF, as well as a HIPAA Authorization Form, prior to completing any study procedures (e.g. wearing the SAM, filling out the questionnaires) and prior to any data collection (e.g. medical history information abstracted from the medical record).

The study coordinator will initiate the informed consent process at an in-person appointment, either before or after a scheduled clinic visit, or at an alternative time that is arranged between the coordinator and the subject. Sites may follow IRB-approved methods for obtaining informed consent, such as consent by telephone and mail, fax, and/or email. The study coordinator will use study aides focused on education during the informed consent process, both to inform subjects of the study procedures and clarify any questions the subject might have. Patients are encouraged to ask questions to the study coordinator, and can also request to talk to the PI about any questions or concerns he/she may have. All subjects will be informed (both by the study coordinator and by text in the consent form) that he/she is not obligated to participate in the study and that it is strictly voluntary. The informed consent process should ensure that there is no penalty for not participating in a clinical trial and that treatment will not be compromised if individuals do not participate or if they cease participation at any time.

The study coordinator will also give patients the option to read the consent form out loud together or give the patient time during a clinic or alternative visit to read the consent alone. Potential subjects who read the consent form but are unsure of participating can ask to have additional time to consider study participation. The study coordinator will arrange a time to meet with the patient again; the meeting time will be based on the subject's availability and when he/she is scheduled for surgery. The study coordinator may also arrange an alternative method to receive the ICF (e.g. mail, fax, or email). Subjects will be asked, ideally, to sign the consent form no less than one to two weeks prior to surgery to ensure they are able to wear the SAM for a 7-14 day time period. Subjects who are unwilling or unable to sign the consent form approximately 7 days before surgery can still participate in the study, but will not wear the SAM. Subjects may be enrolled anytime preoperatively.

Once a subject signs the consent form, the study coordinator also signs the form and then provides a copy to the subject. The original signed consent form will be stored in a binder inside of a locked file cabinet in a locked office. Only the research team members will have access to these consent forms. All sites will maintain copies of subject consent forms with the exception of Harborview Medical Center. Consent forms signed by subjects from the VAPSHCS and Harborview Medical Center will be stored at the RR&D Center (Building 101, GW010) at the VAPSHCS.

We do not anticipate that subjects will need to be re-consented in order to fulfill study participation. While it is possible that changes may occur to the study procedures, subjects will only be re-consented if it is required by a site's IRB. In the event the research team receives additional funding to follow-patients beyond the 24-month mark, subjects will be informed of the study extension and given an opportunity to provide verbal consent to continue their participation or opt out. Subjects' verbal consent or refusal will be documented in a hard copy of the verbal script used to inform them of the study extension. Subjects will only be asked to sign a revised consent form if it is required by a site's IRB.

3.H.2 INFORMED CONSENT DOCUMENT

A copy of the IRB approved consent form from the Coordinating Center can be found in Appendix A.

The subject and a witness who is not a researcher must sign and date the ICF. Additionally, the researcher obtaining consent and the Site PI also sign and date the ICF. Subjects will receive a copy of the signed consent form. The original signed consent form will be stored in a locked filing cabinet inside of a locked office. Sites will maintain copies of signed consent forms. The VAPSHCS will store consents from VAPSHCS subjects and consent forms from subjects at Harborview Medical Center. The source documents should indicate that informed consent was obtained, along with the date of signing. Source documentation may vary by site; some sites may be required to enter an electronic research note into the medical record while other sites may place an enrollment note in the patient's research file. Sites will follow individual IRB requirements for source documentation.

The consent forms will be maintained locally and will be destroyed in accordance with the individual IRB requirements. All sites, at a minimum, will retain signed consent forms for three years following closure of the study. This is an NIH policy requirement.

3.H.3 HIPAA AUTHORIZATION

Participating sites will follow local IRB requirements for HIPAA authorization form format; the HIPAA form may be a separate document from the informed consent, or may be included in the informed consent document. Subjects are required to sign a HIPAA form in order to participate in this study.

A copy of the IRB approved HIPAA Authorization Form from the Coordinating Center can also be found in Appendix A.

Participation in this study requires that research team members have access to/collect the following items from subjects:

- Past and present medical information
- Imaging reports
- All personal identifiable information (PII) maintained in the medical record
- The Seattle Institute for Biomedical and Clinical Research (SIBCR) will be provided with subjects' full name, address, phone number, and social security number in order to authorize payment for participation in this study

3. I TREATMENT ALLOCATION

The surgeon will educate the patient (as a part of routine clinical care) on both surgeries regarding superiority of one treatment over another has not been established without making a recommendation, and then ask the patient if he/she has a preference. For those that have a preference, and the surgeon agrees they are suitable for that treatment, they will be introduced to the study first by the surgeon and then by the study coordinator. If they agree to participate, they will enter into the "preferred cohort" study receiving their preferred treatment. Patients that do not have a preference will discuss both treatment options further with their surgeon and then meet with a study coordinator. Prior to February 2014, surgeons asked patients without a preference if they would be willing to participate in random allocation. All randomization efforts failed as the study surgeons and coordinators observed that a majority of patients did have a treatment preference, were familiar with the devices and hardware used for both procedures, or were uncomfortable having a computer select treatment. Coordinators previously used education aids to discuss randomization (see Appendix B). Sites may use any IRB-approved materials (e.g. education aids, websites, videos) to educate patients on arthrodesis and arthroplasty. Once a participant elects arthrodesis or arthroplasty and agrees to participate in the study, a study coordinator will initiate the screening and enrolment process. Screening logs will be maintained locally and electronically. Spectrum Research, Inc. maintains a web-based screening log. This log is hosted on a website that is simple to use, and structured in the same way as the trial. All enrolled subjects are part of the "preference

cohort”, so the study coordinator will select the “Preference” option and enter the subject ID and treatment of choice (arthrodesis or arthroplasty). The study coordinator may proceed with collecting baseline data once the screening log and informed consent process is complete.

The website system will maintain a log of all coordinators or study personnel (who have privileges) who have logged in with a time stamp. The system will also maintain a log of enrolled participants, treatment allocation, surgery month/year, and study ID. Data will be maintained in such a way that reports can be produced routinely that allow the study Steering Committee and DSMB or Safety Monitor to review the treatment allocations per site. Each site coordinator will also maintain a local copy of screening and enrollment logs

3.J.1 BLINDING AND UNBLINDING (NOT APPLICABLE)

Neither study participants nor surgeons will be blinded to the surgical treatment. Effective February 2014, the study design no longer involves randomization.

3.K STUDY INTERVENTION

This is a clinical trial determining the comparative efficacy and safety of ankle arthrodesis and ankle arthroplasty for patients with end-stage ankle arthritis. Arthrodesis and arthroplasty are two current standard of practice procedures used in the treatment of ESAA; they are not investigational interventions. This study is investigating the outcome of these two surgical procedures. Each site's IRB may determine if the surgery is considered a study-related intervention or a standard clinical care procedure. All patients are educated that the risks of surgery are separate from the risks of the study.

The following arthroplasty and arthrodesis approaches, devices, and post-operative rehabilitation protocols will be used consistent with the standard of care provided by each of the participating institutions. In general, all surgeons will continue to use standard surgical protocols. All participating surgeons have at least five years of experience and have performed at least 30 arthroplasty and 30 arthrodesis procedures.

- 1) Ankle arthrodesis: All surgeons will employ a well-established technique of rigid internal fixation.¹⁵ In this technique, the joint is prepared by removing cartilage from the surfaces, the bones are positioned as desired, and screws and/or a plate are attached to compress the bones together and prevent motion. This technique obviates the need for a cast or external support. The patients are allowed to walk with weight bearing aids immediately. Weight is allowed on the limb in increments over the 6 to 12 weeks after surgery. Radiographs are performed at 6 weeks to determine weight bearing status.
- 2) Ankle arthroplasty: Arthroplasty protocols do not vary much between participating centers. Each surgeon uses an anterior surgical approach between the tibialis anterior tendon and the toe extensor group, splints the ankles for 2 weeks and restricts weight bearing for the first 6 weeks. This study includes 5 implants that are FDA approved: the Agility™ Ankle, the Tornier Salto® Talaris Ankle, the Wright INBONE™ Total Ankle, the Scandinavian Total Ankle Replacement (S.T.A.R.®), and the Zimmer® Trabecular™ Metal Total Ankle. The literature suggests that the outcomes are similar among different prostheses^{16 17 18 19}. No aspect of the surgical care will be changed for the purposes of the trial. No aspect of the rehabilitation will be changed for the purposes of the trial.

3.L PARTICIPANT EVALUATIONS AND FOLLOW-UP

As outlined in the study protocol (see section 3.a), we will take a four-step approach to collecting data on CRFs to achieve our Primary Specific Aims. Study coordinators will interview subjects in person or by phone at intervals of baseline (pre-operative) and 3, 6, 12, and 24 months, and, potentially, every 12 months for up to 20 years after surgery. In rare circumstances when the participant is unable to undergo this interview they will be mailed the study information and can complete it at home and mail back to the study coordinator for querying before sending the CRFs to Spectrum Research, Inc. Subjects also wear a SAM and complete an activity log at baseline and at 6, 12, and 24 months after surgery. All SAMs are mailed to the subject from the Coordinating Center, along with a trackable return envelope. After the subject has worn the monitor for the prescribed period, they will mail it back to the Coordinating Center where data is downloaded, stored, and analyzed using the StepWatch3™ software program. Additionally, study coordinators will perform a medical record review of all notes related to foot and ankle care using a chart abstraction CRF at intervals of 1, 2, 3, 6, 12, and 24 months, and, potentially, every 12 months for up to 20 years after surgery. Any expected AEs will be recorded on the post-operative factors section of the CRFs and will be logged (on the Adverse Event Log Form) for study purposes. Unanticipated problems and SAEs will also be tracked and will be appropriately reported to the Coordinating Center and IRB at the local site.

3.L.1 TIMELINE AND VISIT SCHEDULE

Figure 2 outlines the timeline and visit schedule for subjects in this study. Note that the baseline and follow-up evaluations will occur within the following windows:

- Baseline: anytime preoperatively, up to the day of surgery
- 3 month $\pm$ 1 month
- 6 month $\pm$ 1 month
- 12 month $\pm$ 2 months
- 24 month $\pm$ 4 months
- Every additional 12 months $\pm$ 4months, for up to 20 years post-op

3.L.2 SCOPE

Small differences in study visits may occur between participating sites. Sites will ensure that all study visits adhere to individually approved IRB protocols while also adhering to the MOOP. Copies of the sites' IRB-approved recruitment plans are kept on file at the Coordinating Center.

Baseline visit: Site study coordinators are responsible for conducting the baseline interview prior to surgery with patients. The baseline interview can occur any time before surgery. We will take a four-step approach to collecting questionnaire data on CRFs to achieve our Primary Specific Aims. (1) Study coordinators will conduct the baseline interview with subjects during a scheduled preoperative clinic appointment. (2) For subjects who are unable to complete the interview during the clinic appointment, study coordinators will arrange a time to complete the interview with the patient by phone. (3) Alternatively, patients may elect to fill out the CRF during a clinic visit and a study coordinator will immediately check each page of the CRF for completeness. (4) Patients who are unable or unwilling to complete the interview in person or by phone will have the opportunity to take the CRF home before surgery and return or mail it back to the study coordinator. This last step will be used as a last resort. Study coordinators at participating sites will check the CRF for completeness and call the patient to obtain any missing or questionable data.

During the baseline visit, site study coordinators will explain and demonstrate how to wear a SAM, but all SAM materials are exchanged via trackable shipping service between the Coordinating Center and the

subjects. A member of the research team from the Coordinating Center will contact the patient over the phone to let him/her know that someone will be mailing the SAM, instruction sheet, and activity log through a trackable shipping service. Subjects receive a trackable return envelope to return the monitor and activity log.

3 month follow-up visit: Site study coordinators are responsible for conducting the 3 month follow-up interview (± 1 month from target follow-up date). Study coordinators will take the four-step approach to collecting questionnaire data on CRFs. Subjects do not wear a SAM at the 3 month follow-up.

6 month follow-up visit: Site study coordinators are responsible for conducting the 6 month follow-up interview (± 1 month from target follow-up date). Study coordinators will take the four-step approach to collecting questionnaire data on CRFs. Study coordinators will remind patients how to wear the SAM and explain that a researcher from the Coordinating Center will send the SAM and related documents through a trackable shipping service. Subjects receive a trackable return envelope to return the monitor and activity log.

12 month follow-up visit: Site study coordinators are responsible for conducting the 12 month follow-up interview (± 2 months from target follow-up date). Study coordinators will take the four-step approach to collecting questionnaire data on CRFs. Study coordinators will remind patients how to wear the SAM and explain that a researcher from the Coordinating Center will send the SAM and related documents through a trackable shipping service. Subjects receive a trackable return envelope to return the monitor and activity log.

24 month follow-up visit: Site study coordinators are responsible for conducting the 24 month follow-up interview (± 4 month from target follow-up date). Study coordinators will take the four-step approach to collecting questionnaire data on CRFs. Study coordinators will remind patients how to wear the SAM and explain that a researcher from the Coordinating Center will send the SAM and related documents through a trackable shipping service. Subjects receive a trackable return envelope to return the monitor and activity log.

Long-term follow up visits (once every 12 months for up to 20 years post-op): Site study coordinators are responsible for conducting the long-term follow-up interviews (± 4 month from target follow-up date). Study coordinators will take the four-step approach to collecting questionnaire data on CRFs.

3.L.3 FOLLOW-UP

Upon study entry, each of the site study coordinators will obtain the following information:

- The subject's mailing address
- Telephone number
- Email address (if approved by local IRB)
- Work, cell, or alternate telephone number (when available)

In addition, study coordinators will ask the subject to provide contact information for 1 or 2 additional persons to act as a point of contact in case the study cannot reach the subject directly. Subjects are not required to provide this information. The study will request the following information about these outside contacts:

- Name
- Telephone number(s)
- Mailing address

- Relationship to subject

Planned study follow-up evaluations occur at 3, 6, 12, and 24 months, and, potentially, every 12 months for up to 20 years after surgery. Subjects will receive reminders (via telephone or mailer) for upcoming study visits from the study coordinator. Study coordinators will remain in contact with subjects no less than every 3 months and will check in with patients either by phone or at a clinic visit to thank them for their study participation, remind them of their next follow-up period, verify/update their contact information, and to verify that no AEs have occurred that were not previously noted in the medical record.

Subjects who choose to withdraw from the study will continue to be followed by chart abstraction until the 24 month follow-up. No additional data is collected for withdrawn subjects who revoke their HIPAA authorization in writing. Withdrawn subjects are followed by conducting a medical record review using a chart abstraction CRF at the scheduled intervals (baseline and 1, 2, 3, 6, 12, and 24 months post-operatively). Subjects who cannot be contacted or who refuse to complete a study visit will not be withdrawn and researchers will attempt to resume data collection at the next follow-up period. Investigators or participants may also initiate subject withdrawal if a subject cancels surgery for the following reasons:

- Surgery is scheduled at another institution (non-study site)
- Insufficient insurance coverage
- Postpone major ankle surgery for several years, possibly have less significant surgery that is not arthrodesis or arthroplasty
- Miscellaneous (e.g., changed mind, other medical co-morbidities)

Subjects withdrawn due to no surgery will not be followed until the 24 month follow-up. However, we will track the number of investigator-initiated withdrawals due to no surgery. Figure 2 details the schedule for initial and follow-up visits. Subjects will be mailed a completion certificate following completion of the final follow-up.

3.L.4 FOLLOW-UP DATA COLLECTION USING REDCAP

In addition to the existing database, follow-up data will be collected through a central data capture system known as REDCap, also referred to as Research Electronic Data Capture. REDCap is a secure, online web application that is built to manage online surveys and questionnaires. REDCap is geared to support online data capture for research studies and operations. Therefore, this application is in compliance with 21 CFR Part 11, FISMA, HIPAA, GDPR, and more. This system has been widely used in thousands of institutions in over 100 countries around the globe. Specifically, the VA's REDCap database to store these data behind their secure firewall, and to ensure best practices in maintaining security of the data. Please note that no PHI or PII will be entered into REDCap. Responses from participants will only be linked to an assigned study ID number.

Follow-up patient reported data may be collected and entered into REDCap using the following methods:

1. Data Collection in-person: if the participant is available in the clinic and the study coordinator has a computer available, they may collect questionnaire data electronically by entering in participant responses into REDCap as the research staff reads out the questions. Alternatively, research staff may collect data by writing down participant responses onto a physical, paper copy of the questionnaire. If this route is taken, research staff must enter data into REDCap and store the paper CRFs in a locked study cabinet. Participants may also refuse to answer questions if they are not comfortable doing so.

2. **Data Collection by Phone:** the study coordinator may contact the participant via a phone call to ask if they are available to complete the questionnaire with research staff. If the participant is available, the study team member will access the secure REDCap database through their internet web browser and navigate to the questionnaire that the participant is expected to complete. The study team member will read the questions from REDCap to the participant. Questions will be read to the participant verbatim and the study team member will enter the participant's responses into REDCap. Participants may ask clarifying questions at any point during the data collection process. Participants may also refuse to answer questions if they are not comfortable doing so. Research staff may try to contact participants through calling the participant's secondary phone number or alternative contact if there have been multiple failed attempts to contact the participant through their primary contact method.
3. **Data Collected via a REDCap Survey Link:** the study site coordinator may send a survey link (clickable) and a unique user identification code to participants via email. Participants with internet access can follow the link to the REDCap survey and use the unique identification code for authentication and survey completion. For those patients who prefer this option, their e-mail will be collected. The surveys can be accessed and attempted for a preset number of times (determined by the data manager), or until the site coordinator has marked the survey as "complete". Survey responses will be tracked using the participant email list, linked to the participants' REDCap record. The REDCap survey process only allows for participants to access the specific CRF data that is requested from them by the site coordinator. Each survey link / user identification code pair will only allow for the review or editing of CRF data until the survey is marked as complete.
4. **Data Collected through mailed questionnaires:** if data collection was performed through physical, paper questionnaires, the study site coordinator will manually enter the survey data directly into the secure VA REDCap through an eCRF, or electronic case report form (i.e., questionnaires, surveys). Hardcopy questionnaires will be stored in locked study cabinets inside locked offices. If the returned questionnaire has missing information, research staff may contact the participant to gather data via telephone call. Participants may refuse to answer questions if they are uncomfortable doing so.

Each site will maintain their own contact and tracking logs which will contain PHI and participant ID numbers so that there is a crosswalk between deidentified data and the study participant. UW will provide the secure login usernames and passwords. The password protected databases will include daily backups of data, which will reside behind the UW firewall in a study specific folder. Individual sites may only access deidentified patient data to the participants that are enrolled at their site only. However, the coordinating site may have access to patient data from all other sites for data analysis purposes. Data are only accessible by research personnel with password access.

The master participant file, which will serve as the "crosswalk" between all participants and their study IDs, will only be accessible for investigators and research staff at the coordinating site at VAPSHCS; participating sites may not have access to this master participant file.

3.M PARTICIPANT RETENTION

Note: Subject honorarium payments for completion of study follow-up questionnaires, past the 24 month follow up, have been suspended due to the lack of study funds; per prior approval subjects are being informed of this change via letter or phone call.

Subjects will receive an honorarium in recognition of their time and effort. A \$25.00 payment is made after the baseline, 3, 6, 12, and 24 month postoperative assessments, and potentially after each additional annual follow-up, for a total of at least \$125.00 throughout the course of the study. We will continue to pay subjects \$25.00 for each completed long-term follow-up as long as our budget permits. During the verbal consent discussion about the study extension we will inform subjects of the possibility that we may have to discontinue these payments even though we will continue our data collection for up to 20 years post-op. Compensation is to encourage continued participation and to offset travel, parking, and any inconvenience. The visit burden for the study is small because the interviews take only 20-30 minutes and a routine clinical follow-up that typically coincides with study follow-up. Subjects can also request to complete the interview by phone or at home. Site study coordinators are responsible for tracking subject payments and ensuring payments are submitted and issued to subjects. Sites follow institutional policies for issuing subject payments (e.g. check, reloadable gift card, direct deposit). Subjects can expect to receive a check or other form of payment in the mail approximately 3-6 weeks after completion of a study period.

Retention efforts start during recruitment and are an ongoing process in order to attain a goal of 90% or higher throughout the follow-up period. During initial and annual training, the PI will emphasize to all personnel, particularly study coordinators, that it is essential to maintain a congenial, respectful, and friendly relationship with all participants. Through informal communication (email and phone calls) and routine conference calls, study personnel at each site will discuss retention rates, potential problems, and key retention factors in order to develop interventional strategies for retention.

Additionally, we will employ the following strategies to maximize retention and minimize loss to follow-up.

- Routine contact: Study coordinators will remain in contact with subjects no less than every 3 months and will check in with patients either by phone or at a clinic visit to thank them for their study participation, remind them of their next follow-up period, and to verify that no AEs have occurred that were not previously noted in the medical record. Study coordinators will attempt to build strong relationships with study patients to ensure satisfaction and retention.
- A letter regarding the importance of ongoing participation and data collection may be sent to subjects. Each site may use their discretion to determine if the letter is needed.
- Regular Steering Committee Meetings: An important agenda item for each meeting will be a review of each sites recruitment and retention numbers. If it appears that a site is posting low recruitment or follow-up rates, and efforts have been made during monthly conference calls and individual site adjustment strategies to improve these, the steering committee will investigate/audit the situation through an in-person or virtual site visit. If an audit or investigation does not lead to improvement or a potential resolution, then the PI reserves the right to terminate the site from the study.

3.N CONCOMITANT MEDICATIONS

Patients will not be excluded for using specific medications. There are no medications being investigated as part of this trial; however, surgeons will be allowed to prescribe medications as part of their normal standard of care. There is no reason to believe that concomitant meds will have any interaction with the established surgical procedures or any reason to terminate a participant for using specific medications. Therefore, concomitant medication information will not be collected or recorded.

3.N.1 SAFETY REPORTING

See the Data and Safety Monitoring Plan (DSMP) for details on safety reporting.

Note: As noted above, surgical and other health related SAE/AE reporting practices involving the Safety Officer, will be suspended after all subjects have completed the 24-month follow-up and the final Safety report has been submitted (anticipated completion in Spring 2018). Collection of this SAE/AE data for study purposes will continue. Reporting of research related SAEs/AEs/Other Problems will continue per each active site's local IRB requirements, however to minimize administrative burden, SAEs/AEs that are not related to the research procedures will no longer be summarized and reported with continuing review; the ankle surgery was standard care, not a research procedure.

An **adverse event (AE)** is defined as any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period but have increased in severity.

Expected AEs are those that might reasonably be expected to occur in this population. These events include the following: immediate post-op pain, complications of anesthesia, superficial wound infections, osteomyelitis and deep infection, intraoperative fracture, nonunion or malunion, malalignment, arthritis in adjacent joints, leg length discrepancy, wound dehiscence or skin slough, reflex sympathetic dystrophy, implant failure, implant migration or subsidence, irritation from ectopic bone around hardware, refracture, superficial peroneal neuropraxia, tarsal tunnel syndrome, amputation, chronic edema, chronic ankle pain, stress fractures, osteolysis, and implant loosening. An investigator may also designate an "other" expected AE based on the patient's medical history or other events related to ankle surgery.

An **unexpected adverse event (UAE)** is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product/device or package insert/summary of product characteristics for an approved product or device).

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research participants or others.

All device failures and malfunctions will be documented on the CRF and reported in the clinical results. A device is considered to have failed if it does not perform according to labeling and/or negatively impacts the treatment when used as directed.

Investigators will use the following severity/seriousness of all AEs will be defined as:

- 1) Mild – the patient is aware of the event or symptom, but the event/symptom is easily tolerated.
- 2) Moderate – the patient expresses sufficient discomfort to interfere with or reduce his/her usual level of activity.
- 3) Severe – Significant impairment of functioning; the patient is unable to carry out usual activities.

If an AE is unexpected **and** is possibly/probably related **and** suggests that the research places participants or others at a greater risk of physical or psychological harm than was previously known or recognized, it is an **unanticipated problem (UAP)**. The NIAMS does not require expedited reporting of UAPs unless the problem meets the definition of an SAE. UAPs are reported to the NIAMS Safety Officer biannually in the Safety Report. Sites should report UAPs to the Coordinating Center within 5 business

days of learning about the problem, and sites should follow individual IRB reporting requirements of UAPs. The IRB form used to report UAPs is sometimes referred to as an Unanticipated Problem Involving Risks to Participants or Others form.

3.N.2 ADVERSE EVENT REPORTING

AE information collected throughout the study will capture all AEs (expected/unexpected, not related, possibly/probably related, definitely related, and serious/not serious). Participating sites are responsible for following their local institution's AE reporting requirements. All AEs will be recorded on CRFs and sites will complete an Adverse Event Log Form (Appendix D) which will be filed with the study coordinator at VAPSHCS for data entry. The Coordinating Center and data manager are responsible for preparing AE reports for the Safety Officer using the NIAMS templates every 6 months, unless otherwise requested. Additionally, AEs will be summarized for study steering committee meetings. See the DSMP for additional details.

3.N.3 SERIOUS ADVERSE EVENT REPORTING

All SAEs require reporting to the PI and to the safety monitoring bodies. Sites must notify the PI and PM at the Coordinating Center of the SAE in a timely manner of learning about an event using the SAE CRF (Appendix D). The Coordinating Center is responsible for reporting the SAE to the Safety Officer and NIAMS through KAI in aggregate every six months as part of the biannual electronic safety report. An action plan proposed by the Safety Officer is then sent to the NIAMS and PI, through the Executive Secretary. The Safety Officer will review the SAE report and determine whether he agrees with the investigator's assessment and whether any further follow-up information is required. Additionally, sites are responsible for meeting all local IRB requirements for reporting SAEs (e.g., the Coordinating Center IRB requires reports to be submitted within 5 business days of learning about the event).

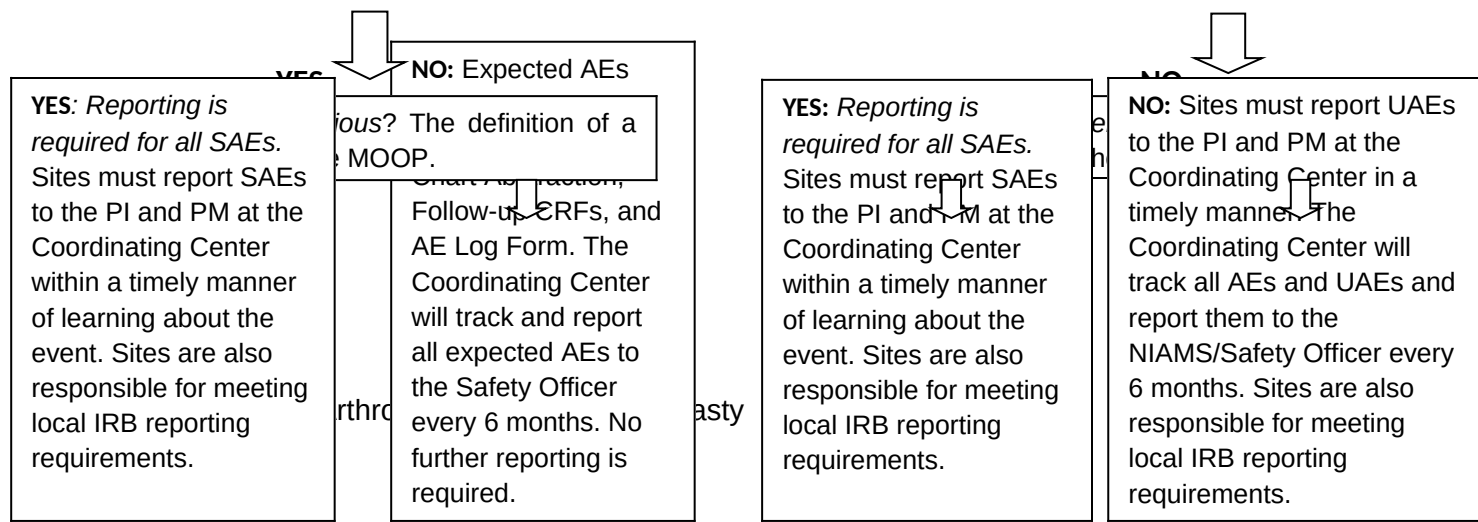
All AEs and SAEs must be followed until resolution or a stable clinical endpoint is reached. All required treatments and outcomes of the AE must be recorded. The type of SAE report (initial/follow-up/final) will be indicated on the CRF. All AEs and SAEs must be followed until:

- AE is resolved and has returned to normal/baseline values or has stabilized.
- Subject is lost to follow-up or has withdrawn consent.
- AE is judged by the investigator to be no longer clinically significant.
- Subject has completed study required follow-ups.
- Study closure.

3.N.4 ADVERSE EVENT REPORTING REQUIREMENTS

Study staff member learns of an adverse event (AE) through medical record review, conversation with the subject, or conversation with the study investigator.

Is the AE *expected*? Expected AEs are defined in the MOOP.





The PI will report all unexpected and expected SAEs, regardless of severity and relatedness, to the NIAMS Safety Officer every six months. Reports are submitted through KAI Research, Inc.

3.0 DATA AND SAFETY MONITORING ACTIVITIES

Note: The DSMB voted to disband, effective November 4, 2016, with safety oversight to continue with a single Safety Officer (Dr. Jonathan Forsberg). As noted above, reporting practices to the Safety Officer, will be suspended after all subjects have past the 24-month data collection. Reporting of SAEs/AEs/Other Problems that are related to the research procedures will continue per each active site’s local requirements; the ankle surgery was standard care, not a research procedure. We anticipate that the final safety report required by the NIAMS will be submitted in the Spring of 2018.

The Safety Officer for this study is appointed by the NIAMS. The Safety Officer is responsible for reviewing the MOOP, routine reports on performance and safety data, and SAE reports. The establishment of an NIAMS-initiated DSMB and the DSMB’s responsibilities and operating procedures are guided by a charter (Appendix C - obsolete).

The Safety Officer plays a crucial role in ensuring the safety and welfare of the patients enrolled in this study. The Safety Officer is responsible for assuring the NIAMS that subjects are not exposed to unnecessary or unreasonable risks and that the investigator conducts the clinical trial according to the highest scientific and ethical standards. The Coordinating Center is responsible for submitting all Safety Reports to its IRB and to the study sites within 5 business days of approval by the study Safety Officer. Local sites will follow local IRB reporting requirements for submitting the Safety Reports.

See the DSMP for details.

3.O.1 GENERIC MONITORING PLANS

See the DSMP for details.

3.O.2 SAFETY OFFICER AND DSMB MEMBERSHIP

The DSMB was disbanded effective November 4th, 2016. A Safety Officer, selected by the DSMB, was appointed to fulfill the role of the DSMB until all subjects have completed the 24-month follow-up. Members of the DSMB were independent of the study and were appointed by the NIAMS. The members of the DSMB were selected to reflect a mix of appropriate clinical expertise and methodological knowledge regarding the study design, monitoring, analysis, and ethical issues of the research project necessary to protect participant safety and the conduct of the study. All members of the DSMB, including

the Safety Officer, signed a *Conflict of Interest Statement*. Contact information for the Safety Officer of this project can be located in the DSMP.

3.P STUDY COMPLIANCE

Initial and annual training, as well as routine meetings among study coordinators and investigators, will occur throughout the course of the study in order to maximize adherence to the protocol and minimize non-compliance (see section 3.e for detailed information on the training). However, deviations to the protocol will be recorded and reviewed in a timely fashion. Furthermore, subsequent training following protocol deviations may occur at the discretion of the Safety Officer (prior to the final report), PI, or NIAMS (prior to exhaustion of grant funds), in order to improve protocol compliance.

A full list of protocol deviations for this study can be found in Figure 3. Examples of common protocol deviations include:

- Enrollment of an ineligible participant
- Failure to obtain Informed Consent and HIPAA Authorization prior to performing any study procedures
- Failure to keep IRB approval up to date
- Collecting data from a participant outside of the appropriate follow-up window

In the event of a protocol deviation, study coordinators at participating sites are responsible for documenting the deviation and ensuring local IRB reporting requirements have been met. Study coordinators are also responsible for reporting the deviation to the PM and PI at the Coordinating Center within 24 hours of the occurrence or within 24 hours of learning of the occurrence. Only protocol deviations that affect participant safety are reported to the NIAMS and the Safety Officer within 24 hours of learning of the event by the Coordinating Center. All protocol deviations are tracked and reviewed during preparation of the biannual Safety Reports. In addition to the Coordinating Center, participating sites should maintain a log (Figure 3) of all protocol deviations so that this information is readily available.

3.Q SOURCE DOCUMENTATION

Source documents for this study include study enrollment/termination notes, operative reports (standard care but record information for research purposes), CRFs for patient reported outcomes, and subject medical records. Data collected on the CRFs will be verified during monitoring visits by examining source documents. Additionally, the SAM subject files will be maintained electronically. Study coordinators will use the activity log completed by subjects to verify data contained on the monitor.

3.Q.1 STUDY FORMS

Copies of the CRFs for this study can be found in Appendix D. Specific details of the questionnaires and survey items contained in each CRF can be found in Figure 2.

Following the informed consent process, data is collected on CRFs preoperatively (baseline) and at 3, 6, 12, and 24 months, and potentially thereafter annually for up to 20 years, postoperatively. Additionally, study coordinators complete the post-operative factors section of the baseline CRF within 2 days following hospital discharge.

Data are collected on CRFs and on SAMs according to the following schedule:

- Baseline: anytime preoperatively, up to the day of surgery

- 3 month ± 1 month (3 month does not use a SAM)
- 6 month ± 1 month
- 12 month ± 2 months
- 24 month ± 4 months
- Every additional 12 months ± 4months, for up to 20 years post-op (No SAM)

3.Q.2 GENERAL INSTRUCTIONS FOR COMPLETING FORMS

- *Recording and shipping information:* CRFs will be completed by all enrolled subjects according to the schedule noted in section 3.q.1. Copies of coded CRF packets are shipped to VAPSHCS via secure and traceable shipping for data entry and storage.
- *Monitoring of the CRFs:* It is the responsibility of the VAPSHCS study coordinator and/ or data manager to inspect the CRFs at regular intervals throughout the study, and to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data before entering it into the study database.
- *Header and footer information:* The header information is consistent on each CRF and does not require any additional information. Footer information must be complete and consistent. The study coordinator should enter the Subject ID at the footer of each page prior to giving the form to the subject. The subject enters the date completing the CRF on the first page and the study coordinator copies the date on the bottom of each page.

Dates should be entered in a DD-MMM-YYYY format using the month abbreviations; **as of November 2017 this specific date system is no longer required on study CRFs, however dates will still be noted on the forms.**

Month	Abbreviation
January	JAN
February	FEB
March	MAR
April	APR
May	MAY
June	JUN
July	JUL
August	AUG
September	SEP
October	OCT
November	NOV
December	DEC

- *Extraneous writing:* The study coordinator will instruct subjects not to write comments on the CRF unless indicated. There are also written directions at the start of each CRF that instruct subjects to only write in the spaces indicated, to only select one answer, and to refrain from writing comments in the margins.
- *Correcting errors:* The study coordinator will instruct subjects to place a single line through any erroneous entry, initial next to the line, and mark the correct response.

- *Completeness:* All CRFs should be completed using blue or black ink. Subjects will be instructed of this and a note-to-file will be filed with the CRF if a subject uses another form of ink or pencil. We will attempt to account for all missing data through a standard data query process. Missing data and data queries are discussed in section 3.u Data Management. Incomplete data may not be available to complete the form for various reasons after the data query process is complete. If an evaluation was not done, the form should be marked ND and a reason should be provided. If information was not available or not applicable, then the form should be marked NAV or NA, respectively.
- *Incomplete or illegible forms:* Incomplete forms that do not have adequate explanation (as described above) compromise the integrity of the study data. Forms that have been received from subjects that are deemed *incomplete* or *illegible* will not be entered into the study database. The study coordinator will contact the subject, either at a clinic appointment or by phone, and ask the subject to complete the interview by phone. If an entire page of the forms cannot be completed (e.g. no parts have any responses), and it is unlikely that it will be completed, draw a diagonal line through the form and write NOT DONE, NOT AVAILABLE, or NOT APPLICABLE, as appropriate. If a form can only be partially completed, but will be completed when the information becomes available, the Clinical Trial Consultant at Spectrum Research, Inc. and/or PM at the Coordinating Center should be consulted. Subjects, study coordinators, and the data manager are made aware that forms cannot be left incomplete or unused without an explanation. Section 3.r outlines the data query process.

A complete set of Completion Guidelines for CRFs will be provided to study coordinators during the site initiation visit.

3.R DATA FLOW

Copies of CRFs are shipped to VA Puget Sound, via secure and traceable shipping for data entry and storage on a regular basis and frequently enough to ensure there is not a back log created (unless no enrollments or follow-ups have occurred). **Sites will retain the original CRF in locked filing cabinets at their respective sites until the study is closed out.** CRFs maintained at VAPSHCS will reside in a locked room with locked filing cabinets..

The data manager is the individual who develops the initial study database and provides periodic troubleshooting services and final data transfer assistance. The data manager communicates regularly with the study coordinators at each site, communicates data collection related issues to the coordinators and investigators, reviews CRFs for accuracy, perform data entry, and initiate data queries.

For data collected on paper CRFs, the VAPSHCS study coordinator will enter study data in a timely manner during the course of the study from the CRF to a secure database. The data cells of the database will mirror the data cells from each CRF. Data entry will be validated (i.e. logic checks including range checks, missing value checks, etc.) both by visual inspection and built-in database programming during the data entry process. Follow-up is considered complete once the patient's follow-up time is accounted for as being censored or they have completed the final follow-up.

To ensure the accuracy of the data, the following processes will be implemented:

1. All forms will be checked for completeness and appropriateness by the VAPSHCS study coordinator. And discrepancies will go through a formal query process described below. The CRFs will not contain any confidential or identifiable patient information.

2. All data collection forms will be inventoried, indicated by date received, form received, and who received; and re-checked for completeness by the VAPSHCS study coordinator.
3. Once the data inventory has taken place, the data will be placed into a data entry queue for double-checking by another member of the research team.
4. Range limits and parameters will be included to reduce the potential of incomplete data and inaccurate data.

Once data are entered, periodic data queries of the database will be run by the data manager and reviewed by the consultant/epidemiologist from Spectrum Research to look for any discrepancies or inaccuracies in the data (e.g., missing and nonsensical values) that may have not been picked up during the CRF screening process. Any discrepancies or inaccuracies will be communicated electronically to the appropriate site study coordinator using a DCF. The site study coordinator will reconcile the query by contacting the patient, the PI, or accessing the source data which may include the medical record. No changes to the original CRF will be made. The coordinator will correct the error or complete the missing value (if possible) in the DCF and send back to the data manager who will correct the database. The DCF will be stapled to the original CRF so that there is a paper trail of all CRF queries and database changes.

3.S RETENTION OF STUDY DOCUMENTATION

NIH policy requires that studies conducted under a grant retain participant forms for three years following completion of the study. However, the Department of Veterans Affairs records retention schedule requires that VA research records be stored for a minimum of 6 years after the study is completed. Study records with PHI/PII will be destroyed using VA approved procedures and in accordance with the records retention schedule after the study is completed. Study data that is de-identified (and labeled with the study assigned ID codes) will be stored indefinitely. A copy of the de-identified data compiled by Spectrum Research Inc. for the VA, will be added to the Center's de-identified data repository (MIRB # 00493; PI: Klute) on an ongoing basis; this will be done via a modification and waiver of consent/HIPAA authorization at the VA Puget Sound.

3.T ADMINISTRATIVE FORMS

Appendix E contains a set of the administrative forms for the study. The following list briefly describes the forms used in this study.

- Facsimile Transmittal Sheet – serves as a cover page for all faxes.
- Telephone Contact Log – serves as a record of all important conversations among study site personnel. Each site will maintain a telephone contact log.
- Screening Log – is a record of *all* patients screened for participation in the study. This log is arranged chronologically and is updated on a routine basis.
- Record of Request for Exemption to Entry Criteria – is a log used to document a participant's exemption to an entry criterion.
- Participant Identification Code List – is a record of the participant's name, medical record number, study ID number, and study entry and exit dates. Due to the confidential nature of this information, this list is stored in a password protected file on a secure VA server (R:\STUDIES\Sangeorzan\00467 NIH Ankle) in a restricted access folder that only the study coordinator, PM, and PI have access to.

- Signature Log – contains the signature of all members of the site study team. It is the responsibility of the PI and PM to a) designate individuals approved to make form entries and changes and b) note the date when any study team member is removed from the team for any reason.
- Site Visit Log – records individuals visiting the site. The most common reasons for visits are site initiation, monitoring, training, and close-out. All sites are responsible for maintaining this log and copies are also sent to the Coordinating Center.

3.U DATA MANAGEMENT

Study records and data collection methodology must enable the reconstruction of the entire study process and verification of the accuracy of all data with sufficient clarity, completeness, and organization that an external reviewer could readily determine that the IRB approved protocol was followed, the data are true and accurate, and that all regulatory responsibilities have been met.

Data entry

The goals of data entry are to enter the data efficiently and accurately into the study database. Data entry should be done within several days of data collection. Entering the data promptly prevents backlogs from accumulating, allows early identification of data collection problems, minimizes possibilities of losses, and allows Spectrum Research, Inc. to generate periodic study reports to keep research staff and investigative site staff informed regarding the progress of the study. It also generates queries regarding missing, out-of-range, or illogical values at a time when it may still be possible to access the subject or return to the source of the data and correct any errors.

The data cells of the database will mirror the data cells from the CRFs. Data entry will be validated (e.g., logic checks including range checks, missing value checks) both by visual inspection and built-in database programming during the data entry process. A subject's electronic study file is not complete until all necessary boxes have been completed.

Data Integrity

Data integrity will be maintained through appropriate security measures. All data will be retrievable, identifiable, and relate to an actual subject. Records and source documents will be retained to enable reconstruction of the study. Audit trails will identify who made the changes, when, and why they were made. All original entries made in source documents/worksheets, CRFs, or databases and all subsequent modifications will be maintained. New entries and/or corrections will not obscure or obliterate the previously entered data. The original data must remain visible within the system. For paper records, this will include drawing one line through the original entry, entering the correction in a way that does not obliterate the original entry, initialing and dating the change.

Role of monitoring for data integrity

In addition to the distant monitoring through a rigorous data query process, a monitor will verify that all data captured in the CRF are supported by source documentation. Refer to section 3.v.2 (site monitoring) for additional details.

In general, the study monitor will bring discrepancies between the CRF and the source document to the attention of the Study Coordinator or other appropriate site personnel. When possible, corrections will be made by the Study Coordinator before the monitor leaves the site. When this is not possible, the monitor will leave a completed DCF, which points out the items that need resolution, with the Study Coordinator. The monitor will not make entries in or alterations to a CRF or source document. Once the discrepancy

has been addressed, the study coordinator can securely mail or e-mail the DCF back to the data manager for updating the database. The data manager will ensure that no changes to the CRF occur after the Investigator has signed the CRF.

Data clarification procedures

The person who discovers the discrepancy in the data will prepare a DCF (i.e., monitor on site or database manager after receiving CRFs) which will be forwarded to the Study Coordinator for resolution. The Coordinating Center monitor will instruct the Study Coordinator to make a copy of the signed and completed DCF before returning the original to the monitor. The Study Coordinator will be encouraged to keep copies of the DCFs with the CRFs (i.e., staple them together). Corrections to the database can then be made but no changes to the CRFs are to be made.

Database management

The central study database will be managed and monitored by Spectrum Research, Inc. and queries will be made on a regular basis to each investigative site as needed to ensure the quality and integrity of the data.

Data should be checked on a weekly basis to ensure that the database is working properly and to identify any errors that need data clarification. The study database will act as a repository for all collected data and will be inaccessible by anyone without pre-assigned confidential password access. Subsets of collected data may be transmitted to a designated recipient or may be transmitted to a second, dedicated database with tightly controlled access requirements. An aggressive database backup schedule will be implemented and closely administered.

Creating a dataset for analysis

Once data collection has ended, a copy of the database will be transferred to statistical analysis software (e.g. Stata or R). Variables will be redefined and new variables created in the data analysis dataset only. The data analysis database will be completely edited and frozen before any final analyses for publication begin. All procedures used to create an analysis-ready dataset will be clearly defined in the data dictionary.

3.V QUALITY CONTROL PROCEDURES

3.V.1 DOUBLE DATA ENTRY

Double data entry will not be used for this study since the data manager consistently checks, validates, and flags data during the data entry and data query process and the database is built with logic and range checks.

3.V.2 SITE MONITORING

The NIAMS has determined these monitoring activities are no longer required, any references to ITHS/study monitor in this MOOP are no longer applicable; see email documentation 8/2/2017.

Periodic site monitoring will occur throughout the course of the study. Site monitoring ensures the rights and safety of participants, confirms that the study is following Good Clinical Practice (GCP) guidelines, ensures the maintenance of required documentation, verifies adherence to the protocol, monitors the quality of the data collected, and ensures accurate reporting and documentation of all AEs and SAEs.

Independent monitoring, separate from the Safety Officer, was recommended by the NIAMS. Per NIAMS recommendations, the study monitors will only visit sites that do not have an adequate internal

monitoring/auditing process. The study monitors are two employees from ITHS, part of the University of Washington. ITHS has a contract with SIBCR for monitoring services. In accordance with applicable regulations, GCPs and VA RR&D SOPs, a study monitor will contact the site at approximately one year after starting study enrollment to schedule a site initiation visit for reviewing the protocol and data collection procedures with site staff. A study close-out visit will take place after the last subject attends their last follow-up at each institution. The monitor will have a frequent communication with each of the investigative sites. During these contacts, the monitor will:

- Review regulatory binders;
- Verify IRB approvals and documents are current;
- Check the progress of the study;
- Review study data collected;
- Conduct source document verification;
- Identify any issues and address their resolution.

This will be done in order to verify that:

- Data are authentic, accurate, and complete;
- Safety and rights of subjects are being protected.

The goal of site monitoring is to maximize recruitment, achieve accountability (e.g. study completed, died, refused f/u, etc.) of all patients enrolled, ensure patient rights are being protected, and ensure data integrity.

Site investigators and study coordinators must ensure that the monitor has access to all study documents, including source documents such as the medical record. Following the monitoring visit, a monitoring report is drafted to provide feedback regarding any problems or issues that may have been uncovered during the visit. The report states the problems discovered and describes recommendations for resolving the issues. The report also recommends a timeframe for resolving all problems. Site investigators and study coordinators are responsible for documenting resolutions and communicating the resolution to the monitor. The PI and PM are responsible for submitting the monitoring report to NIAMS and Safety Officer via KAI Research, Inc.

During the first two years, the monitor will perform 100% source document verification of eligibility criteria, primary and secondary endpoints, and AE data. The monitor will perform 25% verification for remaining data elements. Throughout the remaining years of the study, the monitor will perform 25% source document verification of eligibility criteria, primary and secondary endpoints, AE data, and all remaining data elements.

Monitoring visits will occur according to the following schedule:

- Visit 1: at 12 months after first enrollment
- Visit 2: at 24 months after first enrollment
- Visit 3: at 36 months after first enrollment
- Visit 4: at 48 months after first enrollment
- Visit: annually until study close out

3.W REPORTS

Routine reports prepared by the Coordinating Center and the statistician are an important quality control tool. The study coordinator and/or research assistant at each site is responsible for preparing monthly reports on NIAMS templates that describe target and actual enrollment by site, individuals screened with

reasons for screen failure, and enrollment status of participants (enrolled, active, completed, discontinued treatment, lost to follow-up). If applicable, monthly reports will also summarize any AE or SAE reports submitted since the last meeting. The PM at the Coordinating Center is responsible for preparing monthly aggregate reports of the individual site and overall progress of the study. The data manager and epidemiologist from Spectrum Research will assist in these reports and may also produce additional reports upon request from the PI, Safety Officer, or NIAMS. Additionally, the data manager and study statistician will prepare periodic reports of the data to document completion rates, retention rates, and rates of missing data.

Site investigators and study coordinators are responsible for ensuring that reporting requirements of their local institution and local IRB are met throughout the course of the study. IRB reporting requirements at annual review of this research project will likely vary among sites. Site study coordinators can consult with the PM, PI, or consultant at the Coordinating Center if they are unsure how to satisfy an IRB reporting requirement.

3.X STUDY COMPLETION AND CLOSEOUT PROCEDURES

As noted above, the NIAMS has determined these monitoring activities are no longer required, any references to ITHS/study monitor in this MOOP are no longer applicable.

Prior to the Study Termination Visit

Prior to the Study Termination Visit, the Monitor will perform a comprehensive review of the activities at the site and will:

- Schedule a visit with Investigator(s) and study personnel.
- Send a confirmation letter outlining the purpose of the visit and items for discussion.
- Review the trip report from the previous visit to follow-up on items that are outstanding or action items that need attention.
- Review SAEs.
- Review drop-outs.
- Review outstanding data management issues.
- Gather any documents or materials necessary for the visit.
- Request that all remaining documents be completed and made available for retrieval, including CRFs and DCFs.
- Final SAE information.

Conducting the Study Termination Visit

- Perform a detailed review of all documents and subject records generated from the conduct of the study.
- Resolve any issues remaining from the Periodic Site Visits.
- Ensure the progress of any subject requiring additional follow-up has achieved a satisfactory resolution.
- Resolve any unresolved entry violation or have the Investigator include an explanatory comment on the "Investigator's Comment" page of the CRF.
- Ensure a completed CRF remains on site for each subject enrolled in the study.
- Resolve all remaining data clarification issues and confirm that they have been signed by the appropriate person.
- Return any remaining CRFs and/or data clarifications.
- Inform the study coordinator that data queries generated will still be forthcoming.

- Ensure study site personnel understand record retention requirements for the data.

Study files – To ensure completeness of the study records and documentation, the Monitor will inspect the Investigator's files. The Monitor will ensure:

- A signed copy of the informed consent form is present for each subject enrolled in the study. Any irregularities concerning the informed consent forms which have not been previously documented will be discussed in the Study Termination Visit Trip Report.
- The documents in the Regulatory Documents Binder are present and complete,
- Remind the Investigator of his/her obligation to retain the study records in accordance with local facility standards
- Explain that in the event the Investigator retires, relocates, or for any reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records must be transferred to another person who will accept the responsibility for the records. Notice of such transfer should be given in writing to the Coordinating Center.

Final Study Status Report – The Monitor will ensure that the Investigator completes a final study status report and sends a copy to his/her IRB and to the Coordinating Center.

Final meeting with Investigator and Study Coordinator – The Monitor should make every effort to meet with the Investigator and appropriate study staff to discuss the findings of this visit. The Monitor should:

- Summarize the accomplishments for the entire study.
- Summarize any remaining problems or issues.
- Reach agreement on corrective actions that may be necessary.
- Remind the Investigator of his/her obligations concerning records retention.
- Review publication policy.
- Remind the Investigator that he/she should notify the Coordinating Center if an audit or inspection from an outside entity is planned.

Follow-Up to the Study Termination Visit

Following the Study Termination Visit, the Monitor will document the visit by:

- Completing a Study Termination Visit Trip Report.
- Writing a follow-up letter to the Investigator. The letter should outline what was accomplished during the visit and should note any items that need additional attention.
- Placing copies of the trip report and follow-up letters in the study file.

The Monitor will also:

- Ensure that Data Management has received the CRFs and/or DCFs.
- Place final copies of logs and forms in the study file.

3.X.1 PARTICIPANT NOTIFICATION

Once a participant completes the final follow-up assessment and all data from the SAM and surveys has been entered into the study database, the PM or site study coordinator/research assistant will mail the patient a completion certificate to thank him/her for their time and participation. A representative from the Coordinating Center will also call the patient to ask if he/she wants to be informed of the results when they are made available. A list of patients desiring the results of the study will be maintained by the Coordinating Center. A newsletter describing the results of the study will be mailed to the patient when preliminary results are available. The newsletter or any notification to participants will be approved by the IRB prior to distribution.

3.Y POLICIES

3.Y.1 CONFIDENTIALITY PROCEDURES

The PI, PM, and site investigators routinely outline and enforce participant confidentiality and data security guidelines. Study personnel adhere to the following guidelines in order to protect participant confidentiality.

- Secure data flow procedures: Data identifying participants is not transmitted electronically from sites to the Coordinating Center unless secure PKI-encrypted e-mail is used.
- Electronic files: Electronic files that contain data with patient identifiers are maintained in a password-protected file on a secure drive that only the study staff has access to.
- Paper files: Paper files that contain data with patient identifiers, such as the consent and HIPAA forms, are stored separately from coded data. Additionally, these forms are stored inside of locked filing cabinets located in locked offices.
- Data distribution: Data listings that contain participant identifiers are not distributed among study staff or other individuals associated with the research study. Data that is distributed on paper copy is aggregate data and is organized using NIAMS or other study report templates.
- Data disposal: We do not anticipate needing to dispose of a computer or computer files that contain patient information throughout the course of the study. In the event that a site does need to dispose of files or a computer containing patient information, the guidelines for safe and appropriate destruction will be followed.
- Access: Study records containing both identifiable and coded data are maintained in a secure location inside of a locked office to protect confidentiality. These records should not be accessed to anyone outside of the research team without written consent of the participant.
- Storage: Study forms will be stored in a secure location at all of the sites. The Coordinating Center will follow VA regulations for short and long-term storage of data.
- Passwords: Password protected files at each site will be maintained by the study coordinator and site investigator. Password protected files at the Coordinating Center will be maintained by the PM, study coordinator, and PI. Study staff accessing these files will agree on a shared password and this password should be changed approximately every 6 months to ensure that files remain confidential.
- Training: Study staff at all sites will ensure that NIH and local training requirements are met. At a minimum, staff will take the CITI training course *Human Subjects Protection and Good Clinical Practices*, which highlights important strategies for protecting patient privacy and confidentiality.
- System backups: Data will be stored in a secure study database located on a Spectrum Research server and will be inaccessible by anyone without pre-assigned confidential password access. An aggressive database backup schedule will be implemented and closely administered.
- Sites should make backup copies of electronic data (i.e. screening log, enrollment log, interview tracking log) if backup copies of files are not made automatically. Sites should follow all IRB requirements for making and storing backup files.

If the privacy or security of any of the study data is suspected or known to be breached, each site is required to inform the PI at the VAPSHCS and to follow their site-specific reporting requirements. If a privacy breach is suspected or known to occur at the VAPSHCS, the PI will contact the VA privacy office and/or information security office immediately to report the incident (phone: 206-277-6039; email: PUGPrivacyOfficers/FOIA@va.gov).

3.Y.2 PUBLICATIONS

The PI and site investigators have a responsibility to the public to make study results available as soon as possible. The PI and site investigators are responsible for ensuring that all participating institution, NIH, and NIAMS policies for publication are followed. The PI will check with NIAMS if there are any plans to publish data before the study is over. Any publication must comply with the NIH and NIAMS guidelines for publications, stating acknowledgements, and the NIH Public Access Policy (<http://publicaccess.nih.gov/>).

It is the responsibility of the PI to ensure fair and equitable authorship on publications and ensure that manuscripts endure rigorous review by study staff members and colleagues of the research team who have experience reviewing and contributing to orthopaedic journals.

All participating sites will follow local policies for submissions to academic journals. The VAPSHCS requires that all manuscripts be reviewed and approved by the local Research & Development committee prior to submission to a journal.

3.Z MOOP MAINTENANCE

It is the responsibility of the PI, PM, and Clinical Trial Consultant/Epidemiologist at the Coordinating Center to review, update, and distribute updated copies of the MOOP to all study staff members. However, all study staff are responsible for continuously reviewing the MOOP to ensure that the operating procedures remain accurate. Any staff member discovering errors or necessary modifications to the contents of the MOOP should notify the Coordinating Center so that the appropriate changes can be made and a new version of the MOOP can be distributed.

4.0 RELEVANT WEBSITES

Information Required in NIH Grant Applications:

<http://grants.nih.gov/grants/policy/policy.htm>

NIH Policies for Monitoring Clinical Research:

<http://grants.nih.gov/grants/guide/notice-files/not99-044.html>

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>

<http://grants.nih.gov/grants/guide/notice-files/not99-107.html>

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html>

NIAMS Policies, Guidelines and Sample Documents for Clinical Trials:

http://www.niams.nih.gov/Funding/Clinical_Research/NIAMS_guidelines.asp#3

5.0 FIGURES

FIGURE 1: Prospective cohort design for comparing ankle arthroplasty to ankle arthrodesis in patients with ESAA.

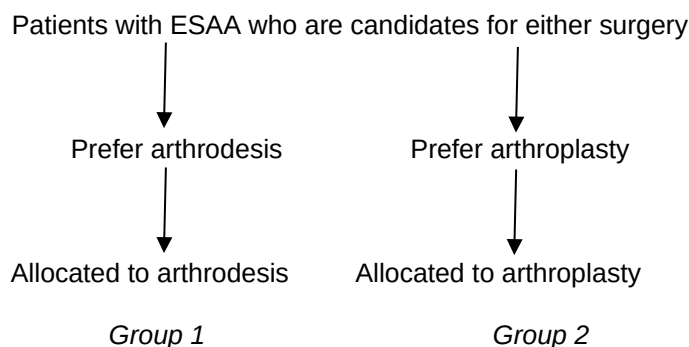


FIGURE 2: Schedule of study visits and evaluations

Visit Description	Screening and Enrollment	Pre-operative Visits	Post-operative Visits		Follow-Up		
Visit period	0 mos.	Baseline (0 mos.)	3 mos.	6 mos.	12 mos.	24 mos.	Long-term; annually
Eligibility questions, basic demographics	X						
Informed consent / HIPAA Authorization	X						
SAM and activity log		X		X	X	X	
CRFs (Comorbidity index, consumption history and demographics)		X			X	X	X
CRFs (FAAM, SF-36, CPG, PLTOP (Seattle only))		X	X	X	X	X	X
ESAA Factors (x-rays)		X					
Medical record review (chart abstraction CRF)*	X		X	X	X	X	X
AEs*		X	X	X	X	X	X
SAEs*		X	X	X	X	X	X

*Medical record and AE review will also occur immediately after surgery and at 1 and 2 months post-operatively.

FIGURE 3:

Protocol Deviation Log

1. Protocol number & title: _____

2. PI: _____ 3. Site: _____

Protocol Deviation Code	Subject Initials	Subject ID	Date Deviation Occurred (mm/dd/yyyy)	Date Protocol Deviation Form Completed (mm/dd/yyyy)	Contact Person

PROTOCOL DEVIATION CODES

Consent Form:

1. Missing or not obtained

2. Not signed and dated by participant

3. Does not contain all required signatures

4. Outdated, current IRB-approved version not used

5. Not protocol specific consent form

6. Does not include updates or information required by the IRB

Eligibility

7. Ineligible participant enrolled

8. Participant completes study procedure prior to determining whether eligible for the study

9. Occurs outside protocol window

IRB:

10. Not reporting a serious complication, AE, SAE within the required timeframe

11. Approvals are not kept up to date

12. Enrollment/treatment occurs prior to IRB approval period or during a period when “on hold”

13. Reportable SAEs not reported to IRB

Participant:

14. Subject receives wrong treatment

15. Visits occur and/or data is collected outside expected follow-up window

16. Subject entered into another study

Study data and CRFs:

17. Missing, unaccounted for data and/or missing CRFs or other study forms

18. Missing radiology and/or operative reports, chart abstraction forms

19. Forms or data not sent from a participating site to the Coordinating Center

FIGURE 4: *Data Clarification Form*

1. Protocol number & title: _____
2. PI: _____
3. Name & title of the person initiating this query: _____

Subject ID	CRF Page #	Data Query	Resolution
Date documented:		Signature & title of the person completing the resolution:	
_____		_____	
DD-MMM-YYYY			

6.0 LIST OF APPENDICES

Appendix A: IRB approved Informed Consent Form and HIPAA Authorization Form (Coordinating Center, VAPSHCS)

Appendix B: Education aids

Appendix C: DSMB Charter (obsolete)

Appendix D: Case Report Forms

Appendix E: Administrative Forms

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