PROTOCOL COVER SHEET

Immediate Weight-bearing Verses Non-Weight-bearing after Foot & Ankle Surgery: A Prospective Analysis

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ABBREVIATIONS AND DEFINITIONS OF TERMS

NWB	Non-weight-bearing
WB	Weight-bearing
AE	Adverse event
SAE	Serious adverse event

ABSTRACT

In recent years, significant attention has been placed on the safety and efficacy of immediate weight-bearing following foot and ankle surgery. Returning patients to their previous activities as quickly as possible following surgery is always in the mind of providers, but the question of when has been difficult to answer.

Objectives:

The primary objective is to assess if immediate weight-bearing following foot and ankle surgery will yield equivalent, if not superior outcomes to the traditional non-weight-bearing post-operative course, while avoiding the undesirable effects commonly experienced during extended periods of non-weight-bearing. This will be determined by serial radiographs and/or other appropriate imaging modalities, physical exams and using patient self-reported pre- and post-operative SF-36 and AOFAS questionnaires.

Study Design:

Prospective, randomized controlled trial.

Setting/Participants:

Patients will be consented from 5 sites West Penn Hospital, Jefferson Regional Hospital, Forbes Regional Hospital, Bethel Park Surgery Center, and Monroeville Surgery Center and the level of care will include both inpatient and outpatient.

The subjects will be identified/recruited during clinic hours as patients requiring an elective or traumatic foot and ankle surgery. During the clinic hours the primary investigator and/or the co-investigator will obtain full consent from the patient. We will recruit a minimum of 115 participants into each of two study arms, an immediate weight-bearing arm and a non-weight-bearing arm, so 230 participants will be included. Patients will be eligible if they are undergoing elective or traumatic foot and ankle surgery. Exclusion criteria will include any patient less than 18 years of age & over 89, history of foot or ankle surgery on the surgical limb, any degree of diagnosed peripheral neuropathy or peripheral vascular disease, infection, and/or unwillingness to participate at random in one of the two study arms.

Study Interventions and Measures:

We will be assessing the difference in two groups; immediate protected weight-bearing in a CAM walking boot vs strict non-weight-bearing for 6 weeks following foot and ankle surgery. Monitoring will be done by way of clinical follow-up, serial radiographs and/or other appropriate imaging modalities, and patient reported outcomes by way of AOFAS and SF-36 surveys.

Surgical procedures performed on patients included in the study will vary, as will the outcome measures for each procedure. Osseous fusions, including both elective joint fusions and bone healing following trauma, will be assessed by both clinical and radiographic evaluation. Soft tissue procedures, including elective stabilization and traumatic soft tissue repairs, will be assessed clinically and with imaging modalities

deemed appropriate. Complications during the perioperative and post-operative periods, such as non-union, infection, etc. will be included in the outcomes. All participants will also complete AOFAS and SF-36 surveys in the pre-operative and post-operative periods. We will also include return to work, activity, sport, etc. where appropriate.

Table 1: Schedule of Study Procedures

Study Phase	Screening	Surgery	Post-op 2-3 w	Post-op 6-8 w	Post-op 3 m	Post-op 6 m	Post-op 1 yr	Post-op 2 yr	Unscheduled Visits
Visit Number	**1**		**2**	**3**	**4**	**5**	**6**	**7**	
Informed Consent/Assent	**x**								
Review Inclusion/Exclusion Criteria	**x**								
Randomization	**x**								
Demographics/PMH	**x**								
Physical Examination	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
Adverse Event Assessment			**x**	**x**	**x**	**x**	**x**	**x**	**x**
Radiographs/Imagining	**x**		**x**	**x**	**x**	**x**	**x**	**x**	**x**
Complete AOFAS/SF-36 survey	**x**			**x**	**x**		**x**	**x**	

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

There is an ongoing debate within the surgical community as to whether it is best to keep patients who have undergone foot and ankle surgery non-weight-bearing (NWB) for an extended period of time versus allowing them to bear weight early, or on occasion, immediately. The standard for many foot and ankle procedures involving fusion of bone and repair of ligaments and tendons has been to keep the patient completely NWB for 6-8 weeks, or the approximate time it takes for bone and tendon to heal, on average. This standard has been challenged in recent years, with more surgeons allowing their patients to bear weight earlier than previously considered safe. Our aim is to assess if immediate weightbearing following any foot and ankle procedure is equally as safe and effective as an extended course of NWB in patients meeting our inclusion criteria.

1.2 Relevant Literature and Data

The available literature has included a number of different procedures where immediate or early weight-bearing has been allowed. In regards to 1st metatarsal-phalangeal joint fusions, Dayton and McCall reported immediate weight-bearing postoperatively in 42 patients with 47 fusions fixated with 2 crossed screws (n=30), 1 screw and 1 k-wire (n=12), and 2 or more k-wires (n=5). Postoperative evaluation was performed at weeks 1, 2, 4, 6, 9, and 12. The overall union rate was 100%, with an average return to athletic shoes at 6.24 weeks. (1) Mah and Banks described a fixation method a 3 crossing k-wires with immediate weight-bearing in a modified post-op shoe with hallux cutout to restrict loading of the hallux. Twenty-two consecutive cases in 20 patients were retrospectively reviewed. Standard AP and lateral radiographs were used to monitor bone healing, with the pins being removed at 6 weeks and the post-op shoe employed for 8 weeks. Solid fusion was observed in 19 patients (86.36%) between 6-8 weeks postoperative. Two feet (9.1%) had nonunion and 1 foot (4.55%) had a delayed union. (2)

There is also extensive evidence that midfoot fusions such as the Lapidus procedure have had good results following immediate or early weight-bearing. Blitz et al. were able to challenge the traditional postoperative non-weight-bearing period by using a 2 or 3 crossed screw fixation technique and allowing the patient to protected weight bear after approximately two weeks. Using both a curettage joint prep technique by one surgeon and planar resection by another surgeon, the joints were prepped to bleeding bone and then fixated with two crossing screws using lag technique. A third screw was used across the 1st and 2nd cuneiforms depending on surgeon judgment for adequate fixation. The results of these procedures were reviewed retrospectively. Of the 80 feet in which the results were reviewed, protected weight-bearing began at a mean of 14.8 days postop, with 100% going on to successful union at a mean time of 44.5 days. (3) Basile et al. investigated the outcomes of patients undergoing Lapidus who were allowed immediate weight-bearing in a removable boot with those made non-weight-bearing in a short leg cast for 6 weeks. They assessed first intermetatarsal angle and first ray elevation measurement radiographically immediately postoperative and then at the 6-month postoperative visit. In a total of 41 feet, there were no significant radiographic changes between the two groups in regards to radiographic evaluation and no non-unions or mal-unions were observed in either group. (4) Using a plantar oriented plate for Lapidus fixation, Gutteck et al. analyzed results between restricted weight-bearing with floor contact (NWB) and immediate full weight-bearing (FWB), both in short arthrodesis shoes. They reviewed 17 cases in each group and found there was no statistically significant difference in radiographic results, AOFAS scores or visual analog scale scores. They did, however, show there was a significant difference in time to return to work, as the FWB group was fit to return to work at a mean of 30.8 days postoperatively, while the NWB group averaged 57 days. (5)

There is also substantial evidence early or immediate weight-bearing is an alternative following trauma. Maffulli et al. performed a comparative longitudinal study placing patients undergoing open repair of midsubstance Achilles tendon tears into two groups, an

early weight-bearing and ankle mobilization group versus an immobilization group. The immobilization group was non-weight-bearing and underwent cast changes every 2 weeks for 6 weeks until a plantigrade ankle position was achieved, at which point they were advised to bear weight. The early weight-bearing group was placed in a weight-bearing cast for two weeks and encouraged to bear weight as tolerated. A single cast change was performed at 2 weeks and an anterior splint was applied to control dorsiflexion for the next 4 weeks. Both groups attended physiotherapy postoperatively. Results showed the early weight-bearing group had fewer outpatient visits, discarded their crutches after an average of 2.5 weeks and were more satisfied with their surgery. The non-weight-bearing group discarded their crutches at an average of 5.5 weeks. And while the early weight-bearing group attended an average of 6.1 therapy sessions over 2.1 months, the non-weight-bearing group needed an average of 13.6 sessions over an average of 4.6 months. (6) Costa et al performed an additional early study looking at the difference in postoperative outcomes between early weight-bearing and traditional non-weight-bearing. Their randomized controlled trial on operatively treated patients placed patient in one of two groups: one which could immediately weight bear in a carbon-fiber orthosis with three 1.5 cm heel raises (n=23), known as the treatment group, or one which was non-weight-bearing in a traditional plaster cast postoperatively (n=25), the control group. Subjects were evaluated every two weeks for eight weeks; with each visit allowing both the plaster group and the heel raise group to progressively return to a plantigrade position from equinus. Results showed significant differences in time to return to walking and return to stair climbing, in favor of the treatment group, though no difference was observed in time to return to sport or work. (7) Suchak et al. evaluated 98 patients divided into two groups, an early-weight-bearing group or a non-weight-bearing group. Weight-bearing status was validated using a pressure sensor in a fixed-hinge ankle-foot orthosis and assessment was performed at six weeks, three months, and six months. Using the RAND 36-Item Health Survey, health-related quality of life was assessed. Results were significantly better for the weight-bearing group in the domains of physical functioning, social functioning, role-emotional, and vitality scores at six weeks. Patients in the weight-bearing group also reported fewer limitations of daily activities. No re-rupture occurred in either group. (8) Huang et al. performed a systematic review with Meta-analysis of the literature between 1990-2013, and found that postoperative early weight-bearing combined with early ankle motion exercises achieves superior and more rapid functional recovery versus conventional immobilization after surgical treatment of Achilles tendon repair. Of note, they found few advantages when only early ankle motion exercises were applied. (9) Valkering and Aufwerber, with their colleagues, looked at the healing process of Achilles tendon ruptures after surgery in a novel way, when they used in vivo microdialysis to examine healing metabolites. In their prospective randomized (controlled trial, they divided patients into two groups, a post-operative functional weight-bearing mobilization group (n=27) and a non-weight-bearing group placed in a plaster cast (n=29). Both groups underwent direct repair of the Achilles tendon rupture, and were then divided into their postoperative groups. The weight-bearing group was allowed to be weight-bearing in a controlled orthosis, allowing 15-30 degrees of plantarflexion. The non-weight-bearing group went into

a plaster cast for 2 weeks, followed by a boot with traditional wedge progression until they reached a plantigrade orientation after 4 additional weeks. In their microdialysis analysis, they found that the healing tendons in both groups exhibited increased levels of metabolites glutamate, lactate, and pyruvate, compared to the subject's contralateral tendon, but the functional weight-bearing group had a significantly higher concentration of glutamate compared to the non-weight-bearing cast group. This correlated to improved functional outcomes at 6 months, and supported their conclusion that functional weight-bearing enhances early healing response after Achilles tendon repair. (10)

In the review of the literature, two separate systemic reviews were identified, which support early weight-bearing after ankle fracture repair when compared to late weight-bearing or non-weight-bearing for six weeks following surgery. These reviews found no significant adverse results in the early weight-bearing groups, while finding earlier return to previous activities and earlier return to work. (11,12). Additionally, Assal et al. was able to show that, with augmented fixation, early weight-bearing in older patients (greater than 70) with Weber B ankle fractures was a safe and satisfactory method of postoperative care. (13) Starkweather et al. found no malunions or nonunions, and a 9.5% complication rate in patients allowed to be protective weight-bearing following ankle fracture ORIF, while Firoozabadi et al. saw a complication rate of 8% and a loss of correction in only 1 of 26 (4%) patients allowed to immediately bear weight following ankle ORIF . (14, 15) In a randomized control trial, Dehghan et al. divided 110 patients into an early WB group (2 weeks) and a late WB group (6 weeks) and assessed time to return to work, SF-36 scores, and rates of complications. They found no difference in return to work between the two groups, but the early WB group showed significantly improved SF-36 scores on both physical and mental components. Early WB was also found to have similar wound complication rates, with no cases of fixation failure or loss of reduction. The late WB group additionally showed higher rates of hardware removal due to irritation. (19% vs 2%) (16)

In regards to calcaneal fractures, it is commonly understood that three months of non-weight-bearing has been the traditional standard of care following open reduction internal fixation. Both Hyer et al. and Kayali et al. performed retrospective reviews of early weight-bearing following open reduction and internal fixation of calcaneal fractures using locking plate fixation, and their results were significant for no unfavorable effects of early weight-bearing. (17, 18) Park et al. retrospectively reviewed 86 patients with acute fifth metatarsal base fractures, divided into conservatively treated versus operatively treated and then further grouped into early weight-bearing or late. They analyzed bone resorption, clinical union, and AOFAS and VAS scores, with results showing no differences in AOFAS or VAS scores, fewer cases of bone resorption in the early weight-bearing groups and earlier bony unions in the early weight-bearing groups. Their conclusion was early weight-bearing may help this population, regardless of surgical or conservative treatment. (19) Wagner et al. retrospectively reviewed 22 patients who suffered low-energy Lisfranc injuries who were then subsequently treated with percutaneous screw fixation and early weight-bearing

during the third postoperative week. Findings were significant for a complete satisfaction rate of 90.9%, an average AOFAS score of 94, and an average return to work of 7 weeks with return to symptom-free sport activities at 12.4 weeks. (20)

1.3 Compliance Statement

This study will be conducted in full accordance all applicable Allegheny Health Network Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.
The investigators will perform the study in accordance with this protocol, will obtain consent and will report unanticipated problems involving risks to subjects or others in accordance with The ASRI-WPAHS IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine the safety and efficacy of immediate weight-bearing following foot and ankle surgery compared to the traditional non-weight-bearing post-operative course.

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine whether immediate weight-bearing following foot and ankle surgery provides similar or superior results to the traditional non-weight-bearing post-operative course, while reducing the disuse atrophy and length of rehabilitation necessary to recover during the transition to weight-bearing following an extended course of non-weight-bearing. This will be done by way of clinical follow-up, serial radiographs and/or other appropriate imaging modalities, and patient reported outcomes by way of AOFAS and SF-36 surveys.

2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Determine if there are specific procedures better suited to immediate weight-bearing.
- Determine if patient satisfaction is higher in an immediate weight-bearing group compared to NWB.
- Determine if immediate weight-bearing allows earlier return to work and/or sport.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

The study will be a randomized 1:1, controlled trial, prospective in nature, where participants undergoing foot and ankle surgery will be randomly placed into one of two

groups; an immediate weight-bearing group or a non-weight-bearing group. The patients will be randomly placed into the study group and control group if they meet all eligibility criteria. The first patient recruited will be assigned a unique study identifier (i.e., FAI001) and a coin flip will randomize the patient into either the study group (Heads) or control group (Tails). From that point, all patients will be placed into their groups by alternating between the control group and the study group. No bias will be placed on the subject or the procedure in regard to inclusion into a certain research group. Patients will be recruited and should they agree will be consented to the study with two year follow up results.

3.2 Study Duration, Enrollment and Number of Sites

This study will be conducted at 5 investigative clinic sites; West Penn Hospital, Forbes Regional Hospital, Jefferson Regional Hospital, Bethel Park Surgery Center, and Monroeville Surgery. Recruitment will stop when a minimum of 230 subjects are consented. The duration of the study for an individual patient will be two years from the surgery date. This will include the pre-operative assessment, surgery, regular post-operative appointments and a final two year follow-up, as noted in the table in the schedule of study section.

3.2.1 Duration of Study Participation

The study duration will require 7 visits to the clinic plus a surgery day therefore will require a pre-surgical visit/screening, surgery procedural day and six outpatient post-operative visits to the clinics. The entire follow up period will occur over 2 years.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at 5 AHN investigative sites in the United States; West Penn Hospital, Jefferson Regional Hospital, Forbes Regional Hospital, Bethel Park Surgery Center, and Monroeville Surgery Center. Recruitment will stop when at least 115 subjects are randomly included in each of the two study arms. It is expected that approximately 230 subjects will be enrolled.

3.3 Study Population

3.3.1 Inclusion Criteria

1) Males or females age 18 to 89 years
2) Undergoing foot and ankle surgery
3) Must be able to read and understand English and consent for themselves

3.3.2 Exclusion Criteria

1) Diagnosed peripheral neuropathy
2) Diagnosed peripheral vascular disease
3) Documented infection to the surgical extremity
4) Previous surgery to the surgical limb

5) Laboratory abnormalities that indicate clinically significant hematologic, hepatobiliary, or renal disease which would predispose patients to poor healing and/or non-union
6) Subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

Below is a list of all of the procedures to be performed at each visit.

- Informed Consent
- Physical Exam
- Radiographic/Advanced Imaging
- Medical Record Review
    - Review of the medical record will include reviewing the past medical and surgical history, laboratory values, and most recent visits to other health care providers in the standard fashion of any office or inpatient encounter
- Surgical procedure discussed and operative consent
- Pre-operative AOFAS and SF-36 surveys completed

4.2 Surgical Visit

4.2.1 Surgery

- Physical Exam
- Medical Record Review Necessary surgical procedure performed

4.3 Follow-up Phase

Follow-up Visit 1 (2-3 weeks post-op)

- Physical Exam
- Radiographic/Advanced Imagining
- Sutures removed
- Medical Record Review

Follow-up Visit 2 (6-8 weeks post-op)

- Physical Exam
- Radiographic/Advanced Imagining
- Post-op AOFAS and SF-36 survey
- Medical Record Review

Follow-up Visit 3 (3 months post-op)

- Physical Exam
- Radiographic/Advanced Imagining
- Post-op AOFAS and SF-36 survey
- Medical Record Review

Follow-up Visit 3 (6 months post-op)

- Physical Exam
- Radiographic/Advanced Imagining
- Medical Record Review

Follow-up Visit 4 (12 months post-op)

- Physical Exam
- Radiographic/Advanced Imagining
- Post-op AOFAS and SF-36 survey
- Medical Record Review

Follow-up Visit 5 (24 months post-op)

- Physical Exam
- Radiographic/Advanced Imagining
- Post-op AOFAS and SF-36 survey
- Medical Record Review

4.4 Unscheduled Visits

Unscheduled visits necessary to address any post-operative complications will be included in the patients study record. At no time will the welfare of the patient be compromised for the execution of the study. If at any time it is decided that a patient should be withdrawn from one of the two study arms, it will be recorded in the study results.

4.5 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, or AEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study

4.5.1 Early Termination Study Visit

Subjects who withdraw from the study before the 12 month follow-up visit will not be included in the final analysis of the study.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

The following will be abstracted from the medical chart:

- Patient age
- Past Medical history –
  - Diabetic vs non-diabetic
  - Height/Weight (BMI)

- Smoker vs past-smoker vs non-smoker.
- Past surgical history
- Occupation and activities

5.1.2 Physical Examination

Physical examination will include evaluation of the dermatologic neurologic, vascular, and musculoskeletal systems of the lower extremities.

5.1.3 Radiographic/Advanced Imaging

X-rays, CT, MRI, and/or ultrasound will be obtained, when indicated, at certain visits determined by the physician. These imaging modalities will evaluate bone healing, joint fusion, and soft tissue repair integrity.

5.1.4 AOFAS and SF-36 survey

Standardized and validated surveys to assess patient function and satisfaction. The SF36 has proven useful in surveys of general and specific populations, comparing relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. In this study we will use the SF36 to assess patient's perceptions of their health.

6 STATISTICAL CONSIDERATIONS

The purpose of the study is to compare the results of immediate weight-bearing versus non-weight-bearing after foot and ankle surgery.
It is hypothesized that immediate weight-bearing following foot and ankle surgery would provide better patient satisfaction with functional outcomes compared to non-weight-bearing after foot and ankle surgery.

6.1 Primary Endpoint

The primary outcome measures are the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score and the SF-36 Health Survey Score as it pertains to the patient's ankle/foot. These assessments will be given to the patient in the pre-operative and post-operative periods.

6.2 Secondary Endpoints

The secondary outcome measures are the frequency of complications during the perioperative and post-operative periods, osseous healing as assessed by both clinical and radiographic evaluation, and healing outcomes of soft tissue procedures. These results will be analyzed at the end of the follow-up period.

6.3 Control of Bias and Confounding

There will be no predilection towards race, ethnicity, sex or sexual orientation. Individuals included in this study will have limited recruit/selection biased. Because the study is focused on physical functionality of patients it will be isolating those patients having a hindfoot fusion procedure and will be recruited from the Foot & Ankle Institute at Western Pennsylvania Hospital, Forbes Regional Hospital, Jefferson Regional Hospital, Bethel Park Surgery Center, and Monroeville Surgery.

6.4 Statistical Methods

6.4.1 Analysis of Primary Outcome of Interest

All analysis will begin with assessment of the normality of continuous variables using the Kolmogorov-Smirnov test. Normally distributed continuous variables will be reported as means and standard deviations; non-normally distributed data as median and interquartile range. Categorical data will be reported as counts and percentages. The Student's t-test will be used to compare continuous demographic and clinical data between the immediate weight-bearing and non-weight-bearing groups. The chi-square test or Fisher's exact test will be used to compare categorical data between groups. Cronbach's alpha will be used to measure reliability, or internal consistency, of both the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and the AOFAS Ankle-Hindfoot Scale survey (AOFAS). Spearman's rank correlation coefficient will be used to assess the relationship between the physical and mental component scores and the eight subdomain scores from the SF-36 and the pain, function and alignment scores of the AOFAS. SF-36 scores and AOFAS scores will be adjusted for patient age, gender, BMI and presence of diabetes mellitus. Nonparametric tests will be used when data breaks the normality assumption. A value of $p<.05$ on two-tailed testing will be considered statistically significant. Statistical analysis will be performed using IBM-SPSS Statistics, version 24.0 (IBM-SPSS Inc., Armonk, NY).
Using one-way repeated measures analysis of variance (ANOVA), differences over time in radiographic and advanced imaging parameters will be assessed separately for the immediate weight-bearing and non-weight-bearing groups. Two-way repeated measures ANOVA will be used to assess differences over time in these parameters between the two groups. Tukey's test or Dunn's procedure will be used for post-hoc pairwise comparisons, as indicated.

Descriptive statistics on the physical and mental component scores and the eight subdomain scores from the SF-36 will be reported for the immediate weight-bearing and non-weight bearing groups. In order to examine differences in SF-36 scores within each group over time, a one-way repeated measures ANOVA will be conducted to determine if the SF-36 scores are significantly different between visits (e.g., screening, post-operative at 6 – 8 weeks, post-operative at 12 months, and post- operative at 24 months). A two-way repeated measures ANOVA will be conducted to determine if the SF-36 scores are significantly different between the two groups for these same visits. Post-hoc pairwise comparisons using Tukey's test or Dunn's procedure will be performed, as indicated.

Descriptive statistics on the pain, function and alignment component scores from the AOFAS will be reported for the immediate weight-bearing and non-weight bearing groups. In order to examine differences in AOFAS scores within each group over time, a one-way repeated measures ANOVA will be conducted to determine if the AOFAS scores are significantly different between visits (e.g., screening, post-operative at 6 – 8 weeks, post-operative at 12 months, and post-operative at 24 months). A two-way repeated measures ANOVA will be conducted to determine if the AOFAS scores are significantly different between the two groups for these same visits. Post-hoc pairwise comparisons using Tukey's test or Dunn's procedure will be performed, as indicated.

The chi-square test will be used to examine the frequency of complications during the perioperative and post-operative periods, osseous healing as assessed by both clinical and radiographic evaluation and frequency of soft tissue procedures between the immediate weight-bearing and non-weight bearing groups.

Logistic regression analysis will be performed to assess which patient characteristics and surgical characteristics are associated with higher SF-36 scores and AOFAS scores.

Due to the potential small sample sizes associated with the various orthopaedic procedures included in this study, the primary analysis will focus on the comparison of the immediate weight-bearing and non-weight bearing groups. Any analyses associated with an individual orthopaedic procedure will be considered exploratory. Finally, the data will not be adjusted for the center where the procedure was performed.

6.5 Sample Size and Power

The study power calculation is based on the primary endpoints.

Assuming the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score and the SF-36 Health Survey Score (as it pertains to the patient's foot/ankle) are normally distributed in the immediate weight-bearing and non-weight-bearing groups and using an independent-samples t-test with a .05 two-sided significance level, and (absent any prior study results) assuming a "medium" effect size of Cohen's d = 0.40, 200 evaluable patients (100 patients in each group) would give you a power of 80% to detect a true difference in means on the questionnaires, if present. Fifteen patients will be added to each group for the potential of loss to follow-up. Final sample size is 230 patients (115 patients in each group). Sample size was calculated using an a-priori sample size calculator for Student t-tests (2017) available from http://www.danielsoper.com.

[1] "Effect size" is a statistical expression of the magnitude of the difference between two groups (Portney and Watkins, 2000). The standardized mean effect, one type of effect size, expresses the mean difference between two groups in standard deviation units. This is

typically reported as Cohen's "d." Interpretation of effect size depends on the research question. Cohen (1988) defines his effect sizes as: 8 = large (8/10 of a standard deviation unit) .5 = moderate (1/2 of a standard deviation) .2 = small (1/5 of a standard deviation). I would recommend using the "medium" effect size for your project. A medium effect size can range from 0.3 to 0.5.

SAFETY MANAGEMENT

6.6 Clinical Adverse Events

During the course of this study the team will follow the protocol laid out in the IRB. If for any reason the protocol needs changed, appropriate modifications will be submitted to the IRB for permission/approval. Compliance meetings will occur annually to assure that data and confidentiality are being maintained. Clinical adverse events (AEs) will be monitored throughout the study.

6.7 Adverse Event Reporting

All on-site SAEs (AHN or related sites) will be reported to the IRB in accordance with IRB policies. AEs that are not serious will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

6.8 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

The risks associated with the study arm, which is immediate weightbearing following foot and ankle surgery include the potential for the following:

- Excessive Pain with weightbearing on the surgical extremity
- Potential wound complications associated with surgical incision sites
- Possible hardware failure
- Possible non-union, mal-union, or delayed union during osseous healing
- Possible non-healing or delayed healing of soft tissue structures

6.9 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death,

- A life-threatening event (at risk of death at the time of the event),
- Requires inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect in the offspring.

6.9.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with ASRI-WPAHS IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

6.10 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the IRB system and in accordance with the IRB SOP#11. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

6.10.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

7 STUDY ADMINISTRATION

7.1 Data Collection and Management

Data Sources

7.1.1 Initial recruitment of study participants will be at the discretion of the participating surgeons, as they will be involved in the decision to proceed with surgery, along with the patient.

7.1.2 Study participation will in no way affect the surgical decision making of the surgical provider. Once the patient has agreed/consented to participate in the study, the Epic Electronic Medical Record System will be used to record variables such as physical examination, imaging, surgery type, etc. The office visits and operative reports will be used to record the surgeon's observations and interventions.

7.1.3 Paper versions of the AOFAS and SF-36 surveys will be uploaded into the patient charts in Epic on password protected AHN computers. The paper version of these

forms will be kept in a locked file cabinet which is locked in the research coordinators office.

7.1.4 A backup of the data will also be stored on a pass key protected external hard-drive provided by the West Penn Hospital Foot and Ankle Residency Program.

7.1.5 All subjects in each arm of the study will be given a unique study number, linking them to the patient MRN number in the Epic system.

7.1.6 All data will be retained and destroyed after publication in accordance with institutional policy, SOP 072, IRB Record Retention, which is 10 years.

7.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at AHN) before sharing a limited dataset (dates and zip codes). No personal subject identifiers will be used in any presentation or publication.

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on password protected institutional computers only accessed by the research team. The investigators and other site personnel will not use such data and records for any purpose other than conducting this study. All participants will be given random unique study identification numbers corresponding, but not matching, their MRN in the Epic system. The study team will have access to the subject's medical records until the records can be transferred to data sheets containing the appropriate patient study identification number.

The data will be destroyed 10 years after publication in accordance with SOP072. Any breaches in confidentiality or other problems will be identified by the study team and reported to the IRB.

7.3 Regulatory and Ethical Considerations

7.3.1 Data and Safety Monitoring Plan

The principal Investigator (P.I.) will be responsible for the ongoing data safety monitoring and oversight for the study sites. Study progress will be reviewed and submitted to the Institutional Review Board (IRB) annually.

The study would be discontinued if there is clear evidence that subjects in the early weight bearing study arm are encountering higher rates of complications compared to the control arm, non-weight bearing (NWB). This would be determined by an outside statistician (Diane Thompson, LLC) that will review the data and adverse events after the first 10

patients have been enrolled in each study arm. Complications would include evidence of higher than expected non-unions, mal-union, uncontrolled pain, or wound complications, as evaluated for which specific surgical procedures were performed, any potential risk factors the patient carried, and patient compliance within the study protocol, and then treated appropriately for their risk of altered or inferior post-operative care.

7.3.2 Risk Assessment

7.3.2.1 There is a potential risk for loss of confidentiality in this study which will be minimalized by only the research team accessing the research data and the PHI.

7.3.2.2 Unique patient study specific identifiers will be used during data collection.

7.3.2.3 All data forms will be maintained in a locked cabinet in the research coordinator's office.

7.3.2.4 No PHI will be transferred, shared or stored on personal computers.

7.3.2.5 Risk of exposure for X-rays; but the dose involved in general x-rays is minimal.

7.3.2.6 There are no increased risks associated with the control arm of the study, which is a traditional non-weight-bearing period of 6 weeks following foot and ankle surgery. The risks associated with the study arm, which is immediate weightbearing following foot and ankle surgery, include potential pain with weightbearing on the surgical extremity; potential wound complications associated with the surgical incision sites; possible hardware failure; possible non-union, mal-union, or delayed union during osseous healing; and/or possible non-healing or delayed healing of soft tissue structures.

7.3.2.7 Currently, the post-operative course following foot and ankle surgery is subjective, based on the previous experiences of the surgeon performing the surgery. We do not believe that there is any additional risk associated with the control arm of the study, which is to maintain non-weightbearing for 6 weeks following foot and ankle surgery. All of the potential risks, including pain, non-union, non-healing, infection, wound complications, and others are possible regardless of the post-operative course. Additionally, we believe that the risks associated with immediate weightbearing following foot and ankle surgery are minimal, as there is ample evidence of previous success with immediate weightbearing following certain procedures.

7.3.2.8 We will minimize the risk of harm by close follow-up during the post-operative course, utilizing appropriate protective devices during weightbearing following foot and ankle surgery, and thoroughly educating our participants on the warning signs of potential complications, regardless of the study group into which the participant falls.

7.3.3 Potential Benefits of Study Participation

The potential benefits of study participation, namely for those participant randomly placed in the immediate weightbearing group of the study, would be those similar to benefits found in previous immediate or early weightbearing studies performed and mentioned in the literature review. These potential benefits would include:

1. The ability to bear weight on the surgical extremity in a protective boot.
2. Reduced muscle atrophy of the surgical extremity
3. Reduced stress on the non-surgical extremity
4. Reduced necessity of rehabilitation following healing of the surgical extremity
5. Increased quality of life during healing following foot and/or ankle surgery
6. Earlier return to work following foot and/or ankle surgery

7.3.4 Risk-Benefit Assessment

The risks of immediate weightbearing following foot and ankle surgery are not unlike the risks faced with a traditional post-operative course of non-weightbearing. While there may be a minimal increase in risk for complications in the study group, given the potential increase of stress on the fixation constructs, potential tension to the surgical incision, and potential pain associated with weightbearing immediately after surgery, we believe that the benefits outweigh the risks. Increasing quality of life during the post-operative period, while decreasing debility and returning patients to their pre-injury or pre-surgical state sooner than previously expected is a substantial benefit.

7.4 Recruitment Strategy

Patient recruitment will be generated from the clinic sites listed in section 3.2 of the protocol. Initial recruitment of study participants will be at the discretion of the participating surgeons, as they will be involved in the decision to proceed with surgery, along with the patient. Study participation will in no way affect the surgical decision making of the surgical provider. Informed Consent/Assent and HIPAA Authorization

7.5 Payment to Subjects/Families

Subjects will not be paid for participation in the study. All treatments, exams, radiographs and visits are considered standard of care with the exception of the questionnaires which will be distributed at five of their visits.

7.5.1 Reimbursement for travel, parking and meals

Discounted parking will be provided to those subjects/patients that come to the West Penn Hospital clinical site. All other sites provide free parking.

8 PUBLICATION

Principal Investigator and Co-Investigators are part of the AHN and will have complete access to all data for the purpose of publication at study completion. No other outside entities are involved in this research study.

9 REFERENCES

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APPENDIX

Append relevant information.

I. DATA COLLECTION FORMS
   a. See attached

II. APPENDIX
   a. Questionnaires

IMMEDIATE VS DELAYED WEIGHTBEARING STUDY

DATE: _____ VISIT: Pre-Op| F/U: #1 #2 #3 #4 #5

PTID# _____ DATE OF SURGERY: _____

STUDY GROUP: Immediate Weightbearing Non-Weightbearing

AGE _____ GENDER M F BMI _____

HISTORY OF SMOKING None Previous Current If yes, how many packs/day? _____

HISTORY OF DIABETES Yes No If yes, last A1c value? _____

COMORBIDITIES:

RADIOGRAPHIC/ADVANCED IMAGING FINDING: Pre-Op #1 #2 #3 #4 #5

XRAY: _____

_____

CT: _____

MRI: _____

Pre-Op:

AOFAS: VAS:

Follow-up Visit #2 (6-8 weeks Post-Op):

AOFAS: VAS:

Follow-up Visit #4 (12 months Post-Op):

AOFAS: VAS:

Follow-up Visit #5 (24 months Post-Op):

AOFAS: VAS:

Procedure(s):

1st MPJ fusion DMO 1st TMT fusion

LisFranc ORIF Midfoot fusion 5th met ORIF

TNJ fusion STJ fusion PCDO PMGL

Achilles repair FHL transfer FDL transfer

Peroneal repair ATT transfer PTT repair

Fibula ORIF Tibia ORIF Bimal ORIF

Ankle fusion TAR

Other: _____

12/2018 V 1.0

Immediate Weightbearing vs Non-Weightbearing after Foot & Ankle Surgery: A Prospective Analysis

PTID#: _____ Date: _____

AOFAS Ankle-Hindfoot Scale (100 Points Total)

1. **Pain (40 points)**

None	40
Mild, occasional	30
Moderate, daily	20
Severe, almost always present	0

2. **Function (50 points)**

Activity limitations, support requirements

No limitations, no support	10
No limitations of daily activities, limitation of recreational activities, no support	7
Limited daily & recreational activities, cane	4
Severe limitation of daily & recreational activities, walker, crutches, wheelchair, brace	0

Maximum walking distance, blocks

Greater than 6 blocks	5
4-6 blocks	4
1-3 blocks	2
Less than 1 block	0

Walking surfaces

No difficulty on any surface	5
Some difficulty on uneven terrain, stairs, inclines, ladders	3
Severe difficulty on uneven terrain, stairs, inclines, ladders	0

Gait abnormality

None, slight	8
Obvious	4
Marked	0

Sagittal motion (flexion plus extension)

Normal or mild restriction (30° or more)	8
Moderate restriction (15° - 29°)	4
Severe restriction (less than 15°)	0

Allegheny Health Network

SF-36® Health Survey Scoring Demonstration

This survey asks for your views about your health as it pertains to your hindfoot fusion.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. Compared to your pre-operative state, how would you rate your health in general now?

Much better	Somewhat better	About the same	Somewhat worse now	Much worse now
○	○	○	○	○

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c	Lifting or carrying groceries	○	○	○
d	Climbing several flights of stairs	○	○	○
e	Climbing one flight of stairs	○	○	○
f	Bending, kneeling, or stooping	○	○	○
g	Walking more than a mile	○	○	○
h	Walking several blocks	○	○	○
i	Walking one block	○	○	○