SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Total Talus Replacement

Device Trade Name: 4WEB Medical Talar Replacement Device

Device Procode: QNN

Applicant's Name and Address: 4WEB Medical
2801 Network Blvd, Suite 620
Frisco, TX 75034

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H240001

Humanitarian Use Device (HUD) Designation Number: HUD # 21-0474

Date of HUD Designation: August 18, 2022

Date of Notice of Approval to Applicant: 12/27/2024

II. INDICATIONS FOR USE

The 4WEB Medical Talar Replacement Device is indicated for avascular necrosis of the talus in adult patients requiring replacement. The anatomical landmarks necessary for the design and creation of the 4WEB Medical Talar Replacement Device must be present and identifiable on computed tomography scan.

III. CONTRAINDICATIONS

- Use of implant greater than 6 months from date of patient's preoperative computed tomography (CT) scan.
- Degenerative changes in the tibiotalar, subtalar or talonavicular joints.
- Gross deformity in sagittal or coronal planes. More than 15 degrees of varus and valgus deformity in the coronal plane, or more than 50% subluxation anteriorly or posteriorly of the talus in the sagittal plane.
- Patients with an active local or systemic infection.
- Osteonecrosis of the calcaneus, distal tibia or navicular.
- Known history of existing malignancy, or any systemic infection, local infection, or skin compromise at the surgical site.
- Blood supply limitations and previous infections that may prevent healing.
- Physical conditions that would eliminate adequate implant support or prevent healing, including inadequate soft tissue coverage.

- Conditions which may limit the patient's ability or willingness to restrict activities or follow directions postoperatively during the healing period.
- Presence of neurological deficit which would prevent patient postoperative compliance.
- Patients with foreign body sensitivity, suspected or documented material allergy or intolerance. Where material sensitivity is suspected, appropriate tests should be conducted, and sensitivity ruled out prior to implantation.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the 4WEB Medical Talar Replacement Device labeling.

V. DEVICE DESCRIPTION

The 4WEB Medical Talar Replacement (TR) Device is designed to replace a patient's native talus that requires replacement due to disease or injury (see Figure 1). The device is designed using 3D modeling software of a patient's computed tomography (CT) scans.

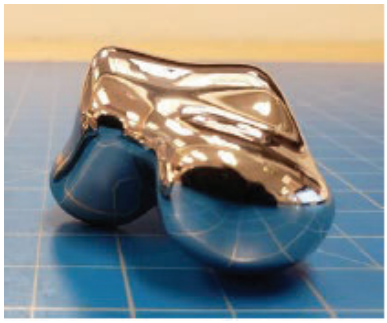

Figure 1: 4WEB Medical Talar Replacement Device

The 4WEB Medical TR Device is made of cobalt-chromium (CoCr) alloy conforming to ASTM F75 and F3213 and is manufactured via laser sintering additive techniques. All surfaces of the device are polished to a mirror finish. The device is then cleaned and passivated per ASTM A967 and is sterilized by the end user via steam sterilization. The patient-matched 4WEB Medical TR Device may be supplied with an instrumentation kit that includes various components for 4WEB Medical TR Device implantation and plastic trials that are used to gauge implant size.

A. Patient-Specific Design Process

The design process for the 4WEB Medical TR Device is a multi-phase process involving the physician, 4WEB personnel, and manufacturing as summarized below:

Project Initiation
A surgeon determines the need for a 4WEB Medical TR Device and completes the 4WEB Medical request form and provides CT data per the 4WEB Medical radiography protocol. The form and CT data are reviewed by the 4WEB Medical Design team for completeness.

Design Input
A case file is created for the 4WEB Medical TR Device. The assigned designer evaluates the CT data and begins processing the images for a virtual meeting with the surgeon where the surgical plan is discussed. The output of this meeting is the information required to design the 4WEB Medical TR Device to the surgeon's preferences and anatomical requirements of the patient.

Design Development
The design inputs are converted into the computer-aided design (CAD) model. A risk assessment, and design rationale are completed.

Design Review and Affirmation
The Design team reviews the 4WEB Medical TR Device design proposal with the surgeon for their approval. The surgeon will either complete the design approval form and return it to 4WEB Medical or provide feedback for design modifications. Once the signed surgeon approval is received, the 4WEB Medical TR Device design advances to the next phase.

Design Transfer
All required documentation including labeling, IFU, design approvals, and CAD models are compiled and the production company is selected.

Manufacture
The devices are additively manufactured, heat treated, finished, and inspected at the selected supplier(s). Any ancillary instrumentation and plastic trial devices will also be manufactured at this time.

Distribution
After 4WEB Medical receives the finished 4WEB Medical TR Device and instrumentation from the supplier, the part will be packaged along with the labeling, order form, and any additional documentation needed. The device is shipped to the end customer where it will be sterilized prior to use.

Use
The surgeon implants one of the 4WEB Medical TR Devices. Unused 4WEB Medical TR Devices will be returned to 4WEB for final disposition.

Service & Surveillance
During this final phase of the TR Device lifecycle, the status of the implant is monitored. Post market surveillance activities are documented to ensure that the device remains implanted to the end user's satisfaction.

B. Additive Manufacturing Process

The 4WEB Medical TR Device is additively manufactured from CoCr using a laser sintering. To ensure an ideal fit with the patient's anatomy, up to three sizes may be simultaneously built on the printing platform: one the expected size, one approximately 10%

larger, and one approximately 10% smaller. Test coupons are manufactured at the worst-case locations of the build platform and tested prior to each device being released.

C. Device Operation and Principles of Operation

The 4WEB Medical TR Device is a solid, metal, anatomical replica of the patient's native talus designed from CT scan images and generated using CAD software, including off-the-shelf software. The prosthetic talus replaces a patient's diseased or damaged talus after a talectomy is performed. The device is made of CoCr and is polished to a mirror finish for articulation with surrounding bones. Anatomical matching allows the 4WEB Medical TR Device to be well positioned within the ankle and congruent with articulating surfaces to preserve joint mobility and maintain leg length.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of avascular necrosis of the talus include grafting techniques, arthrodesis, or below-the-knee (BKA) amputation. The efficacy of these methods varies, with reported good or excellent outcomes ranging from 34%-94% for grafting and 40-85% for arthrodesis [1, 2, 3, 4]. The reported outcomes for BKA when compared to limb salvse techniques are also varied, with some studies suggesting that limb salvage techniques lead to a better physical outcome while other studies suggest the opposite. Regardless of the outcome, all standards of care options have high postoperative complication rates. The failure rate for grafting ranges from 10.5% - 50% with a reoperation rate up to 36% [1,7]. The harvest sites for many of the grafting techniques can also be impacted resulting in a donor morbidity rate of up to 50% [5]. The postoperative complication rate of arthrodesis has been reported as high as 29.9% with a reoperation rate up to 12.9%; this procedure may also leave patients with leg length discrepancy [6]. A BKA has extensive postoperative complications relating to psychosocial outcomes as well as being financially burdensome to the patient compared to the other limb salvage techniques [8].

VII. MARKETING HISTORY

The 4WEB Medical TR Device has not been marketed in the United States or any foreign country.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

- Infection, deep and superficial
- Loosening or migration of the implant
- Nerve damage due to surgical trauma
- Inadequate healing
- Increased pain, soft tissue discomfort or abnormal sensation due to the presence of the device

- Osteosclerosis of adjacent bones
- Cartilage wear and/or arthritis of the joints/bones articulating with the device
- Allergies or other reactions to implant materials
- Loss of anatomic position with rotation or angulation
- Bone resorption or over-production
- Untoward histological responses possibly involving macrophages and/or fibroblasts
- Migration of particle wear debris possibly resulting in a bodily response
- Embolism

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Objectives
The objective of the laboratory studies was to validate the cleaning and sterilization of the device and to ensure the device is biocompatible.

Mechanical Assessment
CoCr material strength is higher than bones in the ankle joint. Furthermore, the 4WEB TR Device is under compression during expected use, thus the expectation is failure of adjacent bones would occur prior to device failure. There were no adverse events reported in the 4WEB TR Device custom device experience or in the retrospective clinical study related to mechanical failure of the 4WEB Medical TR Device. There were also no device fractures or reported in the literature for solid, metallic 3D printed total talus replacement devices. Therefore, no mechanical testing was warranted.

Biocompatibility Testing
The 4WEB Medical TR Devices are additively manufactured from CoCr alloy per ASTM F3213 (ASTM F75 is also accepted as an equivalent reference). After being additively manufactured, the devices are heat treated, polished, and passivated. Passivation, per ASTM F86, removes manufacturing residuals. CoCr has a long history of successful use in medical implants with no significant biocompatibility concerns.

4 WEB Medical completed a biocompatibility risk assessment for the 4WEB Medical TR Device per ISO 10993-1:2018, *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process* and FDA's guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"*, issued September 8, 2023, as an implanted device with permanent duration of contact (> 30 days) with tissue/bone. The risk assessment concluded that the 4WEB Medical TR Device is biocompatible as the final finished device is passivated per ASTM A967 and no other manufacturing process or materials are included before packaging.

Cleaning and Sterilization

The 4WEB Medical TR Device is provided in its finished, final, and clean form, nonsterile packaged to the hospital. The hospital is required to steam sterilize the implant in accordance with the validated steam sterilization instructions as stated in the 4WEB TR Device Instructions for Use. The sterilization process was validated to achieve a sterility assurance level ("SAL") of 10^{-6} using steam sterilization per ANSI/AAMI/ISO 17665-1:2006/(R) 2013, Sterilization of Health Care Products – Moist Heat – Part 1: Requirements for the Development, Validation, and Routine Control of a Sterilization Process for Medical Devices per the overkill method.

X. SUMMARY OF CLINICAL INFORMATION

Study Overview

4WEB Medical completed a retrospective chart review study which examined the clinical and radiographic outcomes of patients implanted with a 4WEB Medical TR Device for the treatment of talus avascular necrosis (AVN) under the Custom Device Exception per Section 520(b). This study was completed in compliance with 21 CFR 50 and 56. The purpose of the clinical evaluation was to demonstrate the safety and probable benefit of the 4WEB TR Device when used in the indicated HUD population. All adult (≥22 years of age) patients who underwent implantation of the 4WEB TR Device between January 1, 2015 and July 15, 2023 and met eligibility criteria at these US sites were included in the study. The study was approved by a centralized IRB (Sterling).

The study enrolled 30 patients (31 devices) from 9 sites, ranging from 1 to 11 patients per site. The study data reflects real world use of the 4WEB Medical TR Device and can be relied on to characterize the safety profile and probable benefit of the 4WEB Medical TR Device. The heterogenous data types presented reflect the outcomes the study team would expect to see across the varying clinical settings. As such, given the retrospective approach, data for each endpoint and at each time point are not available for all patients, and instead, the data presented reflect the type and frequency of data collected in a real-world setting.

No analyses were performed for sex-, gender-, age-, race-, ethnicity-specific subgroups.

Safety Endpoints

The primary safety endpoint was the proportion of patients who underwent a secondary subsequent surgical intervention (SSSI). Other safety endpoints assessed included adverse events (AEs), device or procedure related AEs, AEs categorized by severity, and serious AEs (SAEs). Implant survivorship was also evaluated based on the SSSIs and AEs reported for each patient and assessed qualitatively through review of follow-up notes written by the medical provider.

Probable Benefit Endpoints

The primary probable benefit endpoint was improvement in pain, as measured by the Visual Analog Scale (VAS), at last follow-up compared to baseline. The secondary probable benefit endpoints included ankle range of motion (ROM) and physical function as measured

using the American Orthopaedic Foot & Ankle Society Ankle-Hindfoot Rating system (AOFAS), at last follow-up compared to baseline.

Patient Demographics

A summary of the patient demographics is provided in Table 1. Thirty (30) patients (31 devices) were treated in the study. None of the enrolled patients had bilateral procedures (i.e., a 4WEB Medical TR Device implanted in both the left and right ankles). The study included review of subject records for 14 male and 16 female patients ranging in age from 22 to 71 (mean 47.2) years old at the time of the 4WEB Medical TR Device surgery.

Table 1: Patient Demographics

Age (n=29)	
Mean +/-SD (years)	47.2 +/- 14.2
Range	22 - 71
Gender (n=30)	
Male, n (%)	14 (46.7%)
Female, n (%)	16 (53.3%)
BMI (n=26)	
Mean +/-SD	30.1 +/- 7.1
Range	19.5 – 51.9
Smoking Status (n=27)	
Current, n (%)	4 (14.8%)
Former, n (%)	10 (37.0%)
Never a smoker, n (%)	13 (48.1%)
Laterality (n=31)	
Left, n (%)	15 (48.3%)
Right, n (%)	16 (51.7%)
Both, n (%)	0 (0%)
Race (n=30)	
White, n (%)	16 (53.3%)
Black, n (%)	1 (3.3%)
Not Reported, n (%)	13 (43.3%)
Ethnicity (n=30)	
Hispanic or Latino, n(%)	2 (6.7%)
Not Hispanic or Latino, n (%)	13 (43.3%)
Not Reported, n (%)	15 (50.0%)
Prior Surgeries (n=29)	
0, n (%)	13 (44.8%)
1, n (%)	8 (27.6%)
2, n (%)	5 (17.2%)
$\geq$ 3, n (%)	3 (10.3%)
Primary Indication*	
Avascular Necrosis (AVN), n (%)	29 (93.5%)
Revision of previous talus replacement, n (%)	2 (6.5%)

* Indication information is available for all 31 procedures

Patient Accountability

Table 2 shows the overall number of patients by last follow-up data available, categorized by time cohorts of less than 1 year, 1 year, or 2 years or more. Approximately one-third of patients had their last follow-up in each of the 3 timeframe categories.

Table 2: Patient Accountability

Item	Total Patients	< 1 Yr	1 Yr	≥ 2 Yrs
Last Follow-up	30	9	10	11

Safety Results

4WEB Medical utilized a Clinical Events Committee (CEC) to analyze the safety objectives for the retrospective chart review study. The CEC was comprised of an independent group of experts whose purpose was to advise 4WEB Medical on the safe and effective conduct of this retrospective review, monitor patient safety and the scientific integrity of the retrospective review, and to adjudicate any AEs.

The CEC concluded that no definitive device-related side effect or symptoms were observed for patients who received a 4WEB Medical TR Device. The CEC identified a total of eleven AEs, with one SAE being possibly linked to the device, four SAEs not related to the device but potentially the procedure, and one AE not related to the device but potentially the procedure. These six safety events (potentially device or procedure related) include five SSSI's reported (5/31, 16.1%). The remaining four AEs and one SAE were unrelated to both device and procedure, as shown in Table 3.

Table 3: Categorization of Reported Safety Events

Item	Possibly Device-Related	Possibly Procedure Related	Unrelated
Adverse Events (AE) (n=5)	0	1	4
Serious Adverse Events (SAE) (n=6)	1	4	1
Subsequent Secondary Surgical Interventions (SSSI) (n=5)	*1*	*4*	*0*
Total (n=11)	**1**	**5**	**5**

The five secondary surgeries included one patient with a valgus (turned outward) 4WEB Medical TR Device position which was revised with another 4WEB Medical TR Device, two patients with varus (turned inward) TR Device positions which were revised with either an ankle fusion or a tendo-Achilles lengthening procedure, one patient where their device shifted after implantation which required a second 4WEB Medical TR Device, and a patient who developed arthritis on their tibia which was revised with another 4WEB Medical TR Device. The CEC concluded that none of these SSSIs were directly linked to the 4 WEB Medical TR Device or the talar replacement surgery.

The AEs not requiring a secondary surgery included four patients who reported pain during their post operative follow-ups, all of which were treated in office or with medication, and one patient who began to lose the arch of their foot at their two-year follow-up. The one remaining SAE not related to the device or procedure was one patient who fell and fractured their hip nineteen months post operation.

Implants remained in place for 27 out of 31 (87.1%) devices, demonstrating a high rate of implant survivorship.

Probable Benefit Results

Table 4 shows patient accountability for the analysis-eligible population by length of time to last follow-up for probable benefit outcomes (VAS, ROM, and AOFAS scores).

Twenty-eight out of thirty (93.3%) patients had at least one data point for the evaluation of probable benefit. Probable benefit outcomes (e.g., pain, ROM, and physical function) are measured in relation to date of surgery.

Table 4: Patient Accountability for the Analysis-eligible Population

Item	Total Patients[1]	<1 Yr	1 Yr	2 Yrs
Subject with Patient Reported measures	28	8	10	10
Last Follow-up Visit (by measure)				
Pain (VAS)	23	5	10	8
Range of Motion (ROM)	15	3	5	7
Physical function (AOFAS)	15	3	5	7

[1]Includes patients who had any score (e.g., preoperative or postoperative score) at any time point

Primary Probable Benefit Endpoint: VAS

The primary probable benefit endpoint was the reduction in baseline level pain following surgery using the VAS for pain. Pain scores were collected through retrospective chart review and included VAS scores, ranging from 0-10. Of the 30 subjects, pre- and post-operative VAS pain scores were reported for 20 out of 30 (66.7%) of the enrolled patients. A baseline VAS was available for 20 out of 30 (66.7%) patients and a follow-up score was available for 23 out of 30 (76.7%) patients. Figure 2 and Table 5 present the mean VAS pain changes from baseline for the different follow-up cohorts.

At baseline, the mean VAS pain score for the twenty subjects was 6.4 ± 2.3 and scores ranged from 0 – 10, with 10 representing maximum pain intensity. The mean VAS pain score at last follow-up (n=23) was 3.8 ± 2.8. Mean change from baseline for the twenty subjects with pre- and post-operative VAS pain score was -3.1 ± 3.3. For the cohort analysis, mean improvement for subject with pre- and post-operative VAS pain scores for < 1 year, 1 year, and 2 years cohorts were -2.7 ± 1.2, -3.2 ± 4.1, and -3.2 ± 2.9 respectively.

In instances where both pre- and post-operative VAS pain scores were available, the change from baseline indicated a reduction in pain for all time points.

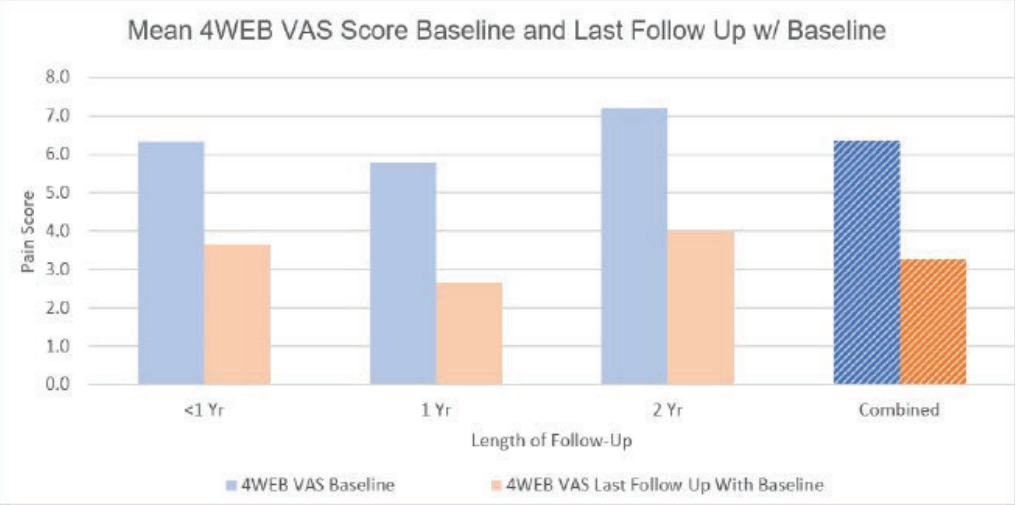

Figure 2: VAS Pain – Mean Baseline and Last Follow-Up w/ Baseline by Duration of Follow-Up

Table 5: VAS Pain Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

Cohort	Assessment	Mean	SD	Median	Range	95% CI
<1 Year	Baseline (n=3)	6.3	3.2	5.0	4 - 10	2.7 , 10.0
	Last Follow Up w/ Baseline (n=3)	3.7	4.0	3.0	0 - 8	-0.9 , 8.2
	Last Follow Up (n=5)	4.6	3.4	6.0	0 - 8	1.6 , 7.6
	Change from Baseline (n=3)	-2.7	1.2	-2.0	-4 – (-2)	-4.0 , -1.4
1 Year	Baseline (n=10)	5.8	2.5	5.5	5 – 9	4.2 , 7.4
	Last Follow Up w/ Baseline (n=10)	2.7	2.4	2.0	0 - 7	1.2 , 4.1
	Last Follow Up (n=10)	2.7	2.4	2.0	0 – 7	1.2 4.1
	Change from Baseline (n=10)	-3.2	4.1	-3.5	-8 – 5	-5.7 , -0.6
2 Year	Baseline (n=7)	7.2	1.6	8.0	5 – 9	6.0 , 8.4
	Last Follow up w/ Baseline (n=7)	4.0	2.6	4.0	1 – 8	2.1 , 5.9
	Last Follow Up (n=8)	4.5	2.8	4.5	1 – 8	2.6 , 6.4
	Change from Baseline (n=7)	-3.2	2.9	-4.0	-7 – 0	-5.4 , -1.1
Combined	**Baseline (n=20)**	**6.4**	**2.3**	**6.5**	**0 – 10**	**5.4 , 7.4**
	Last Follow Up w/ Baseline (n=20)	**3.3**	**2.6**	**3.0**	**0 – 8**	**2.1 , 4.4**
	Last Follow Up (n=23)	**3.8**	**2.8**	**3.0**	**0 – 8**	**2.6 , 4.9**
	Change from Baseline (n=20)	**-3.1**	**3.3**	**-3.5**	**-8 – 5**	**-4.5 , -1.7**

Secondary Probable Benefit Endpoints: ROM

A subset of patients had ankle ROM scores available in their medical records. Of the 30 patients, eleven (11/30, 36.7%) patients had pre- and post-operative dorsiflexion available, with a mean ROM of 9.5 ± 5.7 degrees at last follow up, an improvement of 4.3 degrees on average over the baseline ROM. Figures 3 and Table 6 present mean outcomes for all patients with dorsiflexion ROM data, as well as by cohort based on duration of follow-up period (i.e., < 1 year, 1 year, and 2 years).

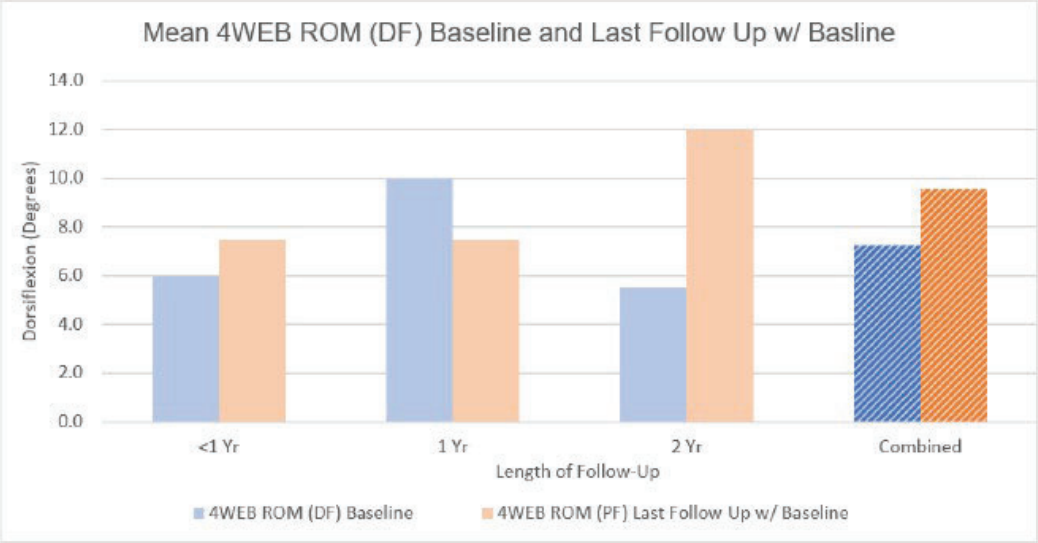

Figure 3: Ankle ROM (DF) – Mean Baseline and Last Follow-Up w/ Baseline by Duration of Follow-Up

Table 6: Ankle Dorsiflexion ROM Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year	Baseline (n=5)	6.0	6.5	0 - 15	0.3 , 11.7
	Baseline w/ Follow Up (n=2)	2.5	3.5	0 - 5	-2.4 , 7.4
	Last Follow Up w/ Baseline (n=2)	7.5	3.5	5 - 10	2.6 , 12.4
	Last Follow Up (n=3)	11.7	7.6	5 - 20	3.0 , 20.3
	Change from Baseline (n=2)	5.0	0.0	5 – 5	N/A , N/A
1 Year	Baseline (n=6)	10.0	11.4	-5 - 20	0.9 , 19.1
	Baseline w/ Follow Up (n=4)	8.8	13.1	-5 - 20	-4.1 , 21.6
	Last Follow Up w/ Baseline (n=4)	7.5	2.9	5 – 10	4.7 , 10.3
	Last Follow Up (n=5)	8.0	2.7	5 - 10	5.6 , 10.4
	Change from Baseline (n=4)	-1.3	10.3	-10 - 10	-11.4 , 8.9
2 Year	Baseline (n=6)	5.5	10.0	-5 - 20	-2.5 , 13.5
	Baseline w/ Follow Up (n=5)	3.6	9.9	-5 - 20	-5.0 , 12.2
	Last Follow up w/ Baseline (n=5)	12.0	7.6	5 - 20	5.4 , 18.6
	Last Follow Up (n=7)	10.0	7.6	0 - 20	4.3 , 15.7
	Change from Baseline (n=5)	8.4	8.4	0 – 22	1.1 , 15.7
Combined	**Baseline (n=17)**	**7.2**	**9.3**	**-5 – 20**	**2.8 , 11.7**
	Baseline w/ Follow Up (n=11)	**5.3**	**10.0**	**-5 - 20**	**-0.6 , 11.2**
	Last Follow Up w/ Baseline (n=11)	**9.5**	**5.7**	**5 - 20**	**6.2 , 12.9**
	Last Follow Up (n=15)	**9.7**	**6.1**	**0 - 20**	**6.6 , 12.8**
	Change from Baseline (n=11)	**4.3**	**9.0**	**-10 - 22**	**-1.0 , 9.6**

The same subset of patients had plantar flexion ROM scores available in their medical records. Of the 30 patients, eleven (11/30, 36.7%) had both pre- and post-operative data available. These patients had a mean plantar flexion ROM of 38.6 ± 13.1 degrees at last follow-up, representing an improvement of 0.5 degrees on average over their baseline ROM and increase of 2.7 degrees over the average of all baseline scores. Figure 4 and Table 7 present mean outcomes for the combined patients with plantar flexion ROM, as

well as by cohort based on duration of follow-up period (i.e., < 1 years, 1 year, and 2 years).

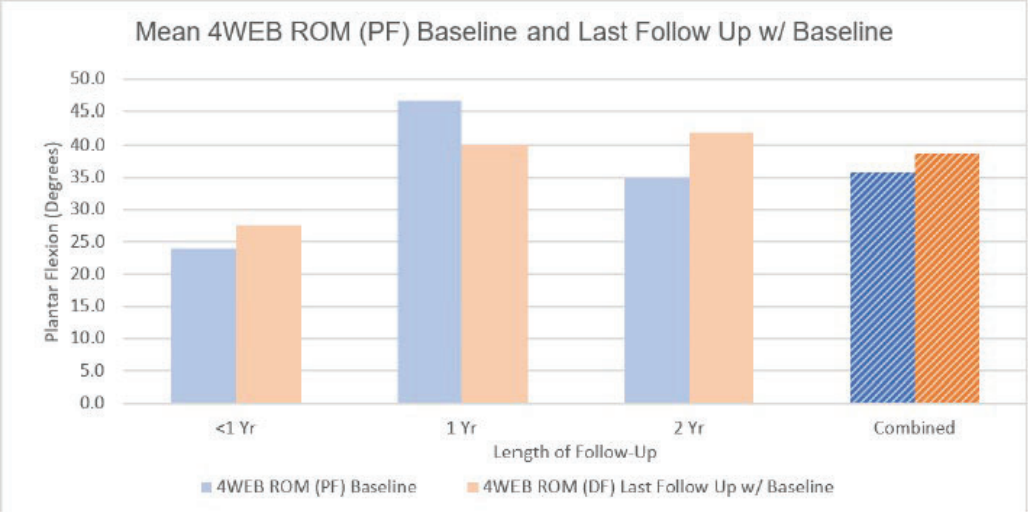

Figure 4: Ankle ROM (Plantar Flexion) – Mean Baseline and Last Follow-Up w/ Baseline by Duration of Follow-Up

Table 7: Ankle Plantar Flexion ROM Mean Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year	Baseline (n=5)	24.0	13.9	10 – 40	11.8 , 36.2
	Baseline w/ Follow Up (n=5)	25.0	21.2	10 – 40	-4.4 , 54.4
	Last Follow Up w/ Baseline (n=2)	27.5	17.7	15 – 40	3.0 , 52.0
	Last Follow Up (n=3)	31.7	14.4	15 – 40	15.3 , 48.0
	Change from Baseline (n=2)	2.5	3.5	0 – 5	-2.4 , 7.4
1 Year	Baseline (n=6)	46.7	5.2	40- 50	42.5 , 50.8
	Baseline w/ Follow Up (n=4)	50.0	0.0	50 – 50	50.0 , 50.0
	Last Follow Up w/ Baseline (n=4)	40.0	11.5	30 – 50	28.7 , 51.3
	Last Follow Up (n=5)	36.0	13.4	20 – 50	24.2 , 47.8
	Change from Baseline (n=4)	-10.0	11.5	-20 – 0	-21.3 , 1.3
2 Year	Baseline (n=6)	35.0	20.7	0 – 50	18.4 , 51.6
Cohort	**Assessment**	**Mean**	**SD**	**Range**	**95% CI**
	Baseline w/ Follow Up (n=5)	34.0	23.0	0 – 50	13.8 , 54.2
	Last Follow Up w/ Baseline (n=5)	42.0	13.0	20 – 50	30.6 , 53.4
	Last Follow Up (n=7)	35.7	16.2	10 – 50	23.7 , 47.7
	Change from Baseline (n=5)	8.0	23.9	-10 – 50	-12.9 , 28.9
Combined	**Baseline (n=17)**	**35.9**	**16.7**	**0 – 50**	**27.9 , 43.8**
	Baseline w/ Follow up (n=11)	**38.2**	**18.9**	**0 - 50**	**27.0 , 49.3**
	Last Follow Up w/ Baseline (n=11)	**38.6**	**13.1**	**15 – 50**	**30.9 , 46.4**
	Last Follow Up (n=15)	**35.0**	**14.0**	**10 - 50**	**27.9 , 42.1**
	Change from Baseline (n=11)	**0.5**	**18.5**	**-20 - 50**	**-10.5 , 11.4**

Secondary Probable Benefit Endpoints: AOFAS

The final secondary probable benefit endpoint was the American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Score. The AOFAS Hindfoot Score is a nine-question survey filled out by both the patient and surgeon where the pain, function, and alignment

of the subject's ankle are rated. The AOFAS scores range from 0-100, with the higher score representing better physical function. Of the 30 patients included in the study, thirteen (13/30, 43.3%) patients had pre- and post-operative AOFAS Hindfoot Scores available. Figure 5 and Table 8 presents the mean change for AOFAS average combined score by cohort based on duration of follow-up period (i.e., < 1 year, 1 year, and 2 years). Patients showed an increase in AOFAS Hindfoot Score post-operatively for all cohorts. The mean change from baseline in AOFAS Hindfoot Score was an increase in 23.1 points.

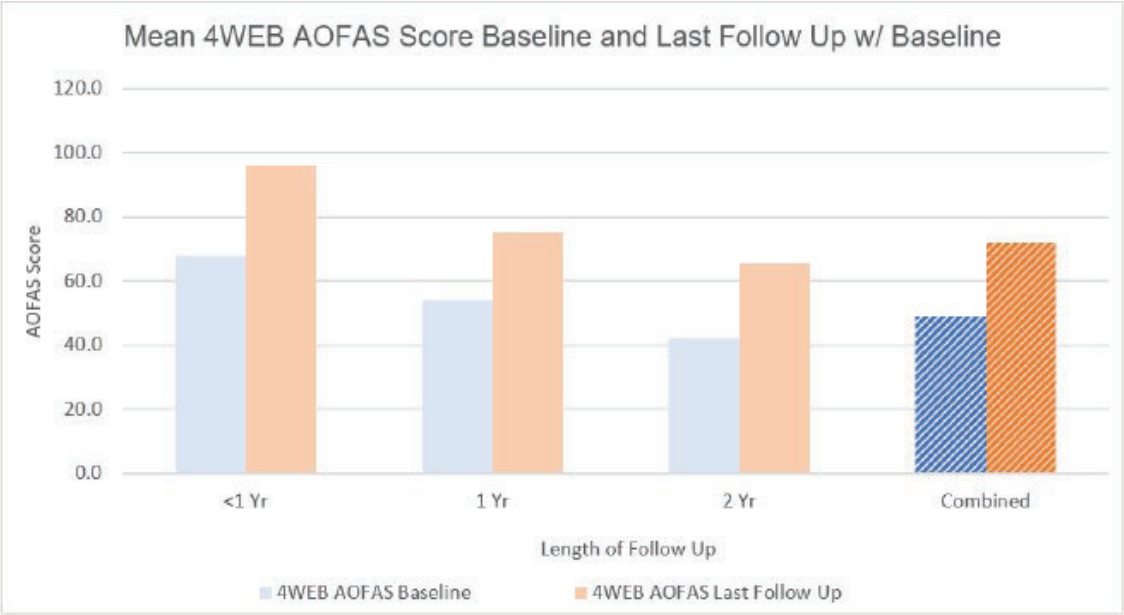

Figure 5: Mean AOFAS Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

Table 8: Mean AOFAS Baseline, Last Follow-Up and Change from Baseline by Duration of Follow-Up

Cohort	Assessment	Mean	SD	Range	95% CI
<1 Year	Baseline (n=1)	68.0	0.0	68	68.0 , 68.0
	Last Follow Up (n=1)	96.0	0.0	96	96.0 , 96.0
	Change from Baseline (n=1)	28.0	0.0	28	28.0 , 28.0
1 Year	Baseline (n=5)	54.0	12.7	39 - 70	42.9 , 65.1
	Last Follow Up (n=5)	75.4	23.1	47 - 98	55.1 , 95.7
	Change from Baseline (n=5)	21.4	28.6	-17 - 59	-3.6 , 46.4
2 Year	Baseline (n=7)	42.3	22.8	0 - 67	25.4 , 59.2
	Last Follow Up (n=7)	65.9	19.9	33 - 87	51.1 , 80.6
	Change from Baseline (n=7)	23.6	29.1	-8 - 79	2.0 , 45.1
Combined	**Baseline (n=13)**	**48.8**	**19.5**	**0 - 70**	**38.2 , 59.4**
	Last Follow Up (n=13)	**71.8**	**21.2**	**33 - 98**	**60.3 , 83.4**
	Change from Baseline (n=13)	**23.1**	**26.4**	**23 – 79**	**8.7 , 37.4**

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The retrospective clinical study included eleven investigators of which none were full-time or part-time employees of the sponsor and eleven investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f).

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

Talar AVN is a cause of significant disability, including pain and mobility inhibition. Treatment options vary based on severity, specifically the presence of talar dome collapse. For more severe cases, treatments are difficult and can delay but unfortunately cannot stop the progression of the disease to talar collapse. At that stage, treatment options have traditionally been limited to salvage procedures of ankle arthrodesis or below the knee amputation. More recently, talar replacement devices have become available and provide patients a treatment option to avoid salvage procedures for talar AVN and the associated significant impact on quality of life, including mobility changes, leg length discrepancy, and loss of the lower leg.

The non-clinical and clinical evaluation of the 4WEB Medical TR Device demonstrate both safety and probable benefit of the device. The real-world clinical data was collected from nine sites and eleven surgeons, which support the generalizability of the data to the general AVN population.

A. Probable Benefit Conclusions

The primary probable benefit endpoint analyzed during the retrospective clinical study of the 4WEB Medical TR Device was the reduction in pain prior to and after surgery. Evidence of pain relief for this study was demonstrated by comparing the level of pain assessed using VAS assessments pre- and post-operatively. All assessments were conducted using a VAS numerical rating scale from 0 (no pain) to 10 (worst pain). The secondary probable benefit endpoints assessed included the ROM of the ankle joint in dorsiflexion and plantar flexion, and the AOFAS Hindfoot Score. The AOFAS Hindfoot Score is a nine-question survey filled out by both the

subject and surgeon where the pain, function, and alignment of the subject's ankle are rated.

The 4WEB Medical TR device demonstrated probable benefit in all four of the primary and secondary endpoints mentioned above.

- Patients in the study reported an improvement in pain at last follow up compared to prior to surgery.
    - On average, patients had a pre-operative VAS pain score of 6.4 (moderate to severe pain), improving post-operatively to 3.3 (mean reduction of -3.1), or mild pain levels [9] with reduction in pain demonstrated across all time points considered (< 1 year, 1 year, 2+ years post-op).
    - A change of 1.00 to 1.36 points on the 10-point VAS scale represents a minimally important difference (MID) in pain severity for subjects undergoing ankle motion preservation surgeries [10, 11].
    - The reduction in pain is notable for a patient population with degenerative disease of the talus facing fusion or lower limb amputation and loss of mobility.

- Patients also demonstrated an improvement in ROM in their affected ankle joint after talar replacement, resulting in an overall increase in entire arc of motion of their ankle joint.

    - The patients who reported a pre- and post-operative dorsiflexion ROM had an average improvement of 4.3 degrees over their baseline value and an increase of 2.3 degrees over the average of all baseline values.
    - The patients who reported a pre- and post-operative plantar flexion ROM had an average improvement of 0.5 degrees over their own baseline value and an increase of 2.7 degrees over the average of all baseline values.
    - The subject device demonstrated an ability to increase ROM arc in the sagittal plane by increasing both dorsiflexion and plantar flexion ROM. The ability for the subject device to maintain sagittal plan ROM postoperatively represents a MID in ROM for subjects undergoing ankle surgeries [12, 13].
    - Any ROM improvement is meaningful in this patient population who otherwise face alternative treatments of arthrodesis which results in a fused ankle with no ankle joint mobility or below the knee amputation and loss of the ankle joint entirely.

- Finally, the results of the AOFAS Hindfoot Scores administered to patients prior to and after surgery indicate that their overall ankle function significantly improved.

- The overall average baseline AOFAS Hindfoot Score for the patients in the study was 48.8/100, improving to 71.8/100 at last follow-up (a 23-point improvement).
- The functional improvement was demonstrated across all timepoints considered (<1 year, 1 year, and 2+ years post-op).
- The average final score of 71.8 indicates that the patient's ankle functionality was capable of returning to a "good" level [14].
- A change of 8.4 to 9.9 points on the AOFAS Hindfoot Score was reported as MID in patients undergoing ankle motion preservation surgeries [10, 11].

Based on these findings, the 4WEB Medical believes the TR Device provides a probable benefit to the patients in the form of meaningful improvements in pain, ROM, and functionality.

B. Safety Conclusions

The risks of the device are based on the data collected in the retrospective clinical study conducted to support HDE approval as described above.

- From all the available data, the risks presented by the 4WEB Medical TR Device failure (fracture) after implantation is very low. There were no reported device failures in the 4WEB Medical clinical study. The overall mechanical strength of the 4WEB Medical TR Device, comprised of CoCr alloy, is far superior to that of the native bone it interacts with.
- From a biological risk perspective, the 4WEB Medical TR Device is considered biocompatible for permanent duration (> 30 days).
- There were no SSSIs directly attributed to the 4WEB Medical TR Device, and only one which was possibly related to the subject device. The number of SSSIs in the 4WEB Medical retrospective clinical study (5/31, 16.1%) is in line or numerically lower as compared to the number of SSSI's presented in the current HDE-approved total talus replacement devices.
- Six patients were affected by AEs, of which zero were directly attributed to the 4WEB Medical TR Device (0/30, 0.0%). The adverse events for these patients included post-operative pain, the subject falling two years after implantation, post operative alignment issues. All of these adverse events are known to be potential risks for orthopedic surgery and are listed in the warnings and precautions of the 4WEB Medical TR Device labeling.
- Implants remained in place for 27/31 (87.1%) devices, demonstrating a high rate of implant survivorship. The four patients who had a device removal included one patient converting to a fusion and three patients who replaced their 4WEB Medical TR Device with a second 4WEB Medical TR Device which has not since been replaced.

C. Probable Benefit-Risk Conclusions

The probable benefits of the device are also based on data in the retrospective clinical study to support HDE approval as described above. The clinical study results are consistent with 4WEB Medical TR Device outcomes reported in the scientific literature and for similar HDE-approved TR devices, supporting the generalizability of the data to the talar AVN population. The safety data were reviewed and adjudicated by experienced orthopedic surgeons and all available data was analyzed. These factors reduce uncertainty with assessment of the probable benefits and risks of the 4WEB TR Device.

4WEB TR Device patients experienced multiple benefits with meaningful improvements in pain, range of motion, and function. On average, the patients presented with moderate to severe pain, averaging a 6.4 out of 10 as measured by the VAS. This pain was meaningfully improved to an average of 3.3, or mild pain post-implantation. The ROM also improved after the 4WEB Medical TR Device implantation, increasing by an average of 4.3º in dorsiflexion and 0.5º in plantar flexion at last follow-up over baseline values. The functional scores using the AOFAS Hindfoot Score showed significant improvement, averaging 48.8 prior to surgery, improving to 71.8 (out of 100 points) after implant. This 23-point score change indicates a meaningful improvement and a "good" level of function.

The probable risks of the device are also based on data collected in a clinical study conducted to support HDE approval as described above. The risks of the 4WEB Medical TR Device documented in the retrospective clinical study are similar to those documented in published literature for TR devices and for HDE-approved TR devices. Adverse events that occurred in the study included post-operative pain, a subject falling two years after implantation, and post operative alignment issues and were present in six of the 31 cases (19.4%). The reoperation rate was low (16.1%), occurring in five out of 31 cases and no cases were directly attributed to the 4WEB Medical TR Device. The reasons for the reoperations were potentially linked to the procedure in four instances and possibly device related in the fifth instance.

1. Patient Perspective

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the HDE for this device.

In conclusion, given the available information above, the data support that for the 4WEB Medical TR Device the probable benefits outweigh the probable risks for adult patients with AVN of the talus requiring replacement. The anatomical landmarks necessary for the design and creation of the 4WEB Medical TR Device must be present and identifiable on CT scan.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. The patients who were analyzed as part of the retrospective clinical study showed meaningful probable benefit with reduction in pain, improvement in range of motion and function. These improvements in functionality allow for a patient to return to a normal lifestyle by preserving their mobility, ability to walk and work, and overall physical health. Moreover, the safety of the device was demonstrated through a low rate of reoperation and no documented device related adverse events.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee because the information in this HDE did not raise any unanticipated safety concerns.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the 4WEB Medical Talar Replacement Device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on December 27, 2024. The final clinical conditions of approval cited in the approval order are described below.

The 4WEB Medical Talar Replacement Device PAS is a multicenter, single-arm, 5-year prospective study for patients who received the 4WEB Medical Talar Replacement Device to evaluate the continued safety and probable benefit of the 4WEB Medical Talar Replacement Device in commercial use in adults (≥ 22 years of age) for treatment of avascular necrosis of the talus.

It is planned for full enrollment of the subjects within 24 months, for a total of 50 subjects. This study will include a minimum of 5 U.S. centers, with a maximum of 20 patients at any one site that meets the selection criteria. The sample size should be adequate to allow for inclusion of a diverse patient population with respect to age, sex, ethnicity, and race. Depending on the population enrolled for the study, oversampling may be necessary to ensure that the population enrolled is sufficiently representative of the US population. Once enrolled, subjects will be followed through 60 months from the time of each patient's index surgery, with interim visits at 3 months, 6 months, 12 months, and annually thereafter.

The primary endpoint for this PAS is a composite of safety and probable benefit, which is the proportion of participants who pass safety and probable benefit outcomes at 5 years post-implantation. The safety endpoint is defined by the absence of a device-related serious adverse event (SAE) and a subsequent secondary surgical intervention (SSSI) on the affected joint. The probable benefit endpoint is defined as device survivorship at 5 years.

Secondary safety endpoints include assessment of device- or procedure-related SAEs, and device- or procedure-related adverse events (AEs). Secondary probable benefit endpoints include assessment of pain using VAS Pain Score, ankle Range of Motion (ROM), American Orthopaedic Foot and Ankle Outcome Scores (AOFAS) Composite score, and AOFAOS Subscales (Pain subscale, Function subscale, and Alignment subscale).

Exploratory endpoints include x-ray assessments to evaluate the presence of AEs, proper location of implant without migration (tibiotalar alignment, talar tilt angle, Boehler's angle, talar declination angle, Meary's angle), absence of subsidence into calcaneus, and health of surrounding soft tissue.

The data will be collected at various timepoints:

Collected at Baseline Only

- Age
- Sex/Gender
- Race/Ethnicity
- Indication for Use
- Surgical History
- Implant Volume

Collected Day of Surgery

- Implant Procedure

Collected at All Timepoints (Baseline, 3-months, 6-months, 12-months and annually thereafter)

- BMI
- Smoking Status
- Working Status
- Ambulatory Status
- Comorbid Conditions
- VAS Pain Score
- AOFAS Composite Score, and AOFAS Subscales (Pain subscale, Function subscale, and Alignment subscale)
- Ankle ROM
- Safety Events: AEs, SAEs, SSSIs
- X-ray (including intraoperative scan)

Descriptive statistics will be presented for all analyses. For continuous variables, means, standard deviations, range, proportions, and 95% confidence intervals will be shown. For categorical variables, frequencies and percentages will be presented.

From the time of study protocol approval, the following timelines for the 4WEB Medical Talar Replacement Device PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months

In addition, you must submit separate periodic reports on the progress of the 4WEB Medical Talar Replacement Device PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the HDE approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports every 3 months in addition to your periodic (6-month) PAS Progress Reports, until FDA notifies you otherwise.
- Submit the Final PAS Report three (3) months from study completion (i.e., last subject's last follow-up date).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

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