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METHODOLOGY

The Functional Ambulation: Standard Treatment versus Electrical Stimulation Therapy (FASTEST) trial for stroke: study design and protocol

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Background: Surface electrical stimulation for foot drop (foot drop stimulation [FDS]) technology has greatly improved over the last decade, leading to increased use in the clinic environment and the community. Despite numerous studies suggesting the benefit of FDS among persons with stroke, there are no randomized controlled trials comparing FDS to standard of care (ankle foot orthosis [AFO]). The Functional Ambulation: Standard Treatment versus Electrical Stimulation Therapy (FASTEST) study is a single-blinded randomized controlled trial with the primary purpose of comparing FDS and AFO among persons with stroke conducted at eleven sites throughout the USA.

Methods: Persons ≥ 3 months poststroke are randomized to wear either FDS or AFO for 30 weeks. After 30 weeks, AFO participants crossover to wear an FDS. All participants are followed for 42 weeks with repeated measures at baseline and Weeks 6, 12, 30, 36, and 42. The primary analysis will compare gait speed between FDS and AFO at 30 weeks. Secondary outcomes span the International Classification of Functioning, Disability, and Health categories and include functional gait, balance, motor control, falls, and quality of life. Tertiary analyses will be performed using Weeks 36 and 42 time points.

Conclusion: This pivotal trial is the first longitudinal randomized controlled trial to compare FDS and AFO in persons with stroke. Further, the results will be the largest single contribution to date on the efficacy of FDS in people with stroke, providing a robust dataset with findings that can be extrapolated for use as guidelines to clinical practice.

Trial registration: clinicaltrials.gov NCT01138995.

Keywords: electrical stimulation, stroke, cerebrovascular accident, rehabilitation, foot drop stimulation, gait

Introduction

Each year 795,000 people experience a new or recurrent stroke in the USA, resulting in 7 million Americans living with stroke.[1] Stroke is a leading cause of serious long-term disability in the USA.[1] In fact, among stroke survivors ≥ 65 years old, 50% had some hemiparesis and 30% were unable to walk without some assistance at 6 months post-stroke.[1] The ability to independently ambulate has been identified as a key determinant for survival.[2] While 65%–85% of patients eventually ambulate independently after stroke,[3–5] the majority of these independent ambulators still walk at speeds considered less than functional for community ambulation,[6] thereby limiting their overall level of social participation.[7] Therefore, interventions to effectively enhance gait have the potential to profoundly impact quality of life poststroke.

One of the most common and frustrating neurological deficits that result from stroke is foot drop. Foot drop is characterized by the inability to dorsiflex the foot sufficiently

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to lift the toes completely off the ground during the swing phase of walking. In addition, the foot on the hemiplegic leg often does not strike the ground in the normal way at initial contact (ie, heel strike).[8] This may cause unstable and slow gait with increased risk of falls. Foot drop during the swing phase also increases walking effort because of compensations required to advance the leg.[9] Additionally, weakness in the dorsiflexor muscles and/or spasticity in plantarflexor muscles has been associated with difficulty with other functional activities such as rising from a chair and has been linked to falls after a stroke.[10–12] It has been reported that foot drop is a persistent form of long-term disability in 10%–20% of stroke survivors.[13]

Conventional, standard of care treatment for foot drop is an ankle foot orthosis (AFO), a plastic or metal support worn on the lower leg. AFOs provide ankle dorsiflexion support during the swing phase and improve knee stability during the early stance phase of gait.[8,14] A recent systematic review of the effects of AFO in stroke had limited conclusive findings due to the lack of rigor and diversity of trials.[15] The long-term effects of AFO use in persons with stroke have not been studied. Since the primary goal of the AFO is to provide support and positioning for weakened muscles and joints, this treatment has several potential limitations. For example, the typical AFO immobilizes the ankle, which may contribute to the development of contracture,[16] and does not allow the person to use residual active foot movement.[14] This potentially limits future recovery of ankle strength and function, promoting disuse atrophy in the hemiplegic lower leg. Solid (ie, unhinged) AFOs also hinder standing from a sitting position as they limit dorsiflexion, and initial foot position is a major determinant of the ability to stand up from a chair.[17] A recent study of people with hemiplegia from stroke who had completed their rehabilitation found that although the use of AFOs improved their gait speed and balance, over 60% of the participants indicated that they prefer not to use their AFO because of aesthetics.[18]

Surface electrically induced dorsiflexion by means of a foot drop stimulator (FDS) has been reported in the clinical literature since the 1970s and has been in clinical use for many years.[19] As an alternative to a traditional AFO, FDS can be used to activate the ankle muscles during walking. Traditional systems consisted of an external pulse generator with a pair of leads connected to surface hydrogel electrodes and another wire running to a heel switch placed in the patient's shoe. These design limitations have been linked to reports of decreased use.[20] Technical advancement to FDS, such as wireless design, reproducible electrode placement via stimulation cuffs, and more sophisticated programming has allowed the devices to be used with greater ease in the clinic and the community. Studies suggest that among persons with stroke, FDS facilitates normal electromyographic activity and decreases flexor–extensor cocontraction; improves symmetry in stance and cycle time; improves knee and ankle kinematics and reduces energy cost; increases cortical activity; increases strength, mobility, and gait velocity; and improves functional ambulation such as walking over varied surfaces and negotiating turns, obstacles, and stairs.[20–43]

The benefits of FDS can be assessed in two ways: orthotic (while using the device) and therapeutic (carryover effects not using the device). The most recent systematic review addressing orthotic effects pooled data from six studies found a significant ($P < 0.05$) increase in gait speed of 0.13 m/second.[21] The most recent meta-analysis addressing therapeutic effects pooled data from three studies using a fixed effects model and found a mean difference in gait speed of 0.18 m/second ($P < 0.01$).[44] Although this cumulative evidence shows benefits of FDS for gait in persons with stroke, to date there have been no randomized controlled trials to compare the effects of FDS to standard of care AFO.

Patient compliance is a critical consideration. A few studies have reported on patients' preference between FDS and AFO. A recent study used a qualitative approach to examine orthotic preferences for people with stroke. Eight of the nine people interviewed preferred using FDS to the AFO, citing reasons of ankle mobility, walking ability, and comfort.[45] After an 8-week FDS intervention, 26 participants who formerly used an AFO significantly ($P < 0.05$) preferred the FDS due to comfort, appearance, and gait quality, distance, effort, and stability.[34] In a similarly designed study among 15 participants with stroke, 13 felt more stable and 14 reported a more normal gait with the FDS compared to AFO.[29] In a cross-sectional study, twelve of 14 participants preferred FDS to AFO, citing improved muscle movement, strength, and gait.[24] Given the magnitude of foot drop in stroke and subsequent functional limitations, more rigorously designed trials are needed to assess the value of these devices in stroke rehabilitation.

The effect of FDS or an AFO on gait can be measured in several different ways, as illustrated in Figure 1. The immediate effect refers to changes in gait that occur when initially wearing the device. A training effect above and beyond the immediate effect may occur as the patient uses the AFO or FDS over time. The therapeutic effect refers to improvements in walking seen even without wearing an AFO or FDS and may result from changes in neural plasticity, peripheral

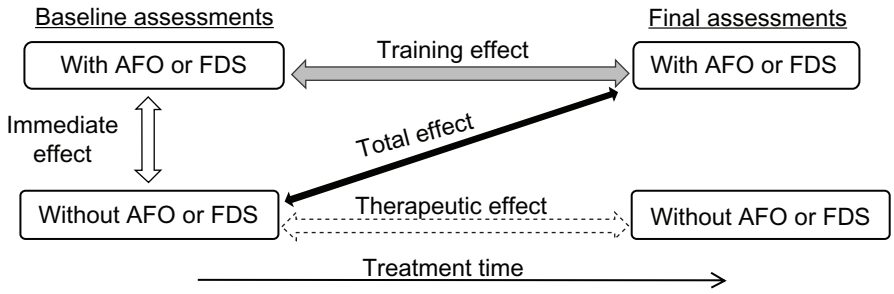

Figure 1 Illustration of possible comparison effects of device (FDS, AFO) on gait.
Abbreviations: AFO, ankle foot orthosis; FDS, foot drop stimulation.

strength, cardiopulmonary system, or other systems. The total effect refers to the changes in gait that occur over time, and encompasses both the immediate and training effects.

The Functional Ambulation: Standard Treatment versus Electrical Stimulation Therapy (FASTEST) trial is designed to compare FDS and AFO for drop foot among people > 3 months poststroke, with a gait speed ≤ 0.8 m/seconds. This is a multicenter, randomized controlled, single-blinded trial. The primary hypothesis is that after 30 weeks, participants randomized to the FDS group will demonstrate greater improvement in gait speed than participants randomized to the AFO group. This hypothesis was based on the anticipated total device effects, encompassing both the immediate and training effects. Other comparisons illustrated in Figure 1 will also be assessed. There are several secondary outcomes including gait function, balance, stroke-specific quality of life, and safety. Tertiary analyses will also be performed using Weeks 36 and 42 time points.

Methods/design

FASTEST is a multicenter, randomized controlled, partial crossover, single-blinded study in which persons ≥ 3 months poststroke are followed for 42 weeks. Participants are randomized to either 30 weeks of wearing a surface FDS (original treatment group) or 30 weeks of AFO (original control group). After 30 weeks, the original control group crosses over to wear the FDS; whereas the original treatment group continues to wear the FDS. The FDS used in this protocol is the NESS L300®, manufactured by Bioness Inc (Valencia, CA, USA) who sponsored this study.

Participants are being recruited from eleven clinical sites across the USA (Figure 2). Each site has obtained local institutional review board approval except one that used Western Institutional Review Board (Olympia, WA, USA). Informed consent occurs during the first visit before any participant information is obtained and before any medical evaluations or baseline testing are performed. After consenting, the participant sign the Health Insurance Portability and Accountability Act authorization form and eligibility is confirmed (Table 1).

Outcomes

Repeated outcome measures are obtained using established, stroke-specific measures at Weeks 0, 6, 12, 30, 36, and 42 (Table 2). Outcomes are measured with and without the device (FDS or AFO) to assess several possible effects, as illustrated in Figure 1. An immediate effect refers to the change in gait that may occur when initially wearing the device: Visit 1 (V1) without device compared to V2 with device. A training effect may occur as the subject uses the orthotic over time: V2 with device compared to V8 with device. A therapeutic effect refers to the change that may occur in walking without the device: V1 without device compared to V8 without device. A total effect refers to the changes in gait that occur over time, and encompasses both the immediate and training effects: V1 without device compared with V8 with device.

Outcome testing is performed by licensed physical therapists who are blinded to the randomization group. To maintain blinding, a nonblinded research team member coordinates outcome testing and all subjects wear loose pants, a lower leg and shoe cover ("gaiter") on the involved lower extremity (to conceal the AFO or FDS cuff and pressure sensor), and an FDS control unit. Standardization of outcome measures is maximized across sites by providing test kits and outcome tester training followed by onsite competency testing.

Primary outcome

Gait speed measured by the 10 m walk test is the primary endpoint for this study. The 14 m course incorporates 2 m at beginning and end to allow for acceleration/deceleration. Both comfortable and "fast" gait speed are measured. The 10 m walk test is reliable in persons with stroke with intraclass correlation coefficient (ICC) values of 0.8–0.98,[46,47] and walking speed has been shown to be a predictor of

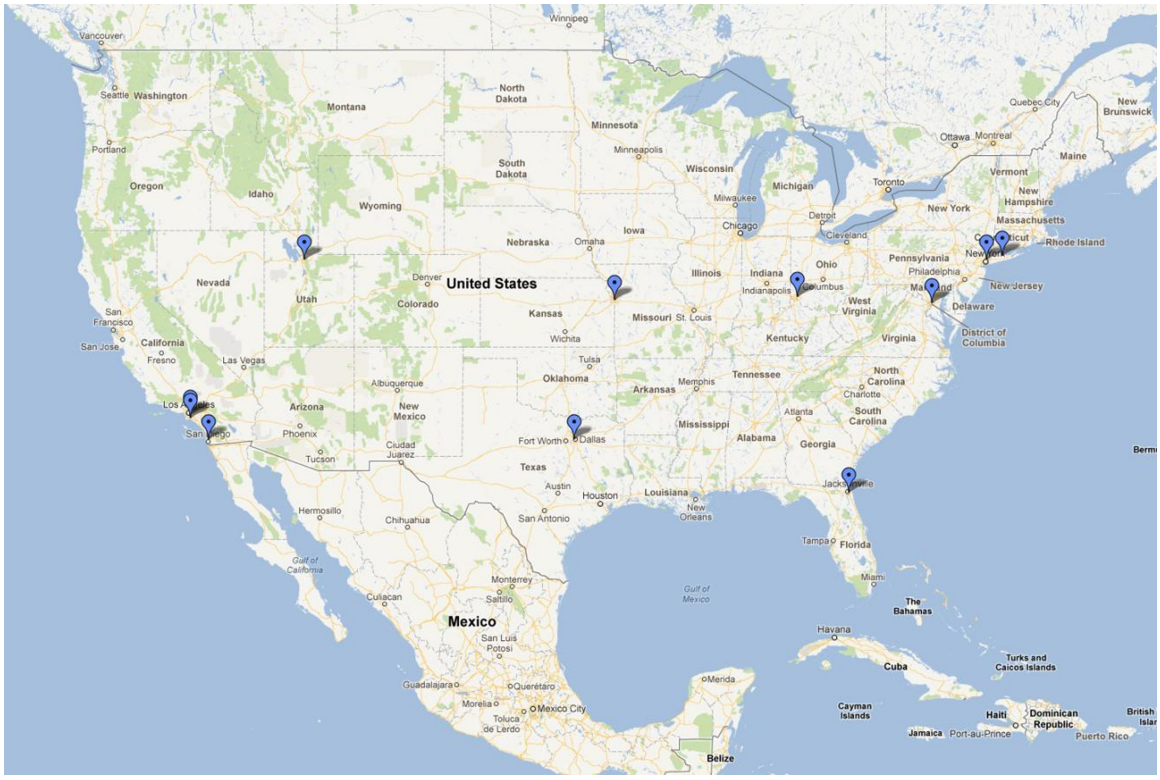

Figure 2 The eleven study sites include: University of Cincinnati, UC Health Drake Center; Weill Cornell Medical College; University of Kansas Medical Center; Long Beach Memorial Medical Center; University of Utah; Sharp Rehabilitation Center; Brooks Rehabilitation Hospital; UT Southwestern Medical Center; National Rehab Hospital; and St Charles Hospital and Rehabilitation.

community ambulation and functional status.[6,49–52] During ambulation outcomes testing, the most commonly used assistive device (>50% time) at the time of assessment is utilized. The amount of assistance provided during each test is assigned using the Functional Ambulation Category,[53–55] although no assistance is provided for the advancement of a paretic limb.

Secondary outcomes

The Timed Up and Go test is used to measure functional mobility. It is reliable and valid among persons with stroke.[48,56] The 6-minute walk test is used to measure functional walking endurance.[57–59] This indoor walking course is on a level, noncarpeted surface measuring a length of 18 m with a 0.5 m turn at each end marked by a cone. One chair is positioned before the start line, one past the 18 m mark, and one to two chairs are staggered along the path at 6 m and 12 m. This test is reliable in persons with stroke with ICC values of 0.97–0.99.[48,60–62] The Berg Balance Scale is used to measure balance. It is a task performance test consisting of 14 items of increasing difficulty graded on a five-point ordinal scale of zero to four (zero = participant is unable to perform task; four = participant is independent in performance of task).[63] The Berg Balance Scale is highly reliable and valid and has been used in many previous studies among persons with stroke.[64–66] The Stroke Impact Scale activities of daily living, instrumental activities of daily living, mobility, and participation subscales are used to measure quality of life. The Stroke Impact Scale and its subscales are valid, responsive, and robust.[67–70] The Functional Reach Test is used to measure functional balance,[71] and is reliable, valid and responsive.[72–74] The Lower Extremity Fugl-Meyer motor subscale is used to measure motor recovery and impairment. The Fugl-Meyer has been reported to be an effective tool to quantify motor impairment in stroke survivors and to stratify severity of impairments,[75] and is reliable with ICC values of 0.89–0.96.[76–78] Falls are obtained by self-report from participants and/or their caregivers retrospectively 6 months prior to baseline and at each study visit during the 30-week intervention period. Circumstances regarding each fall are collected, including any injury or medical attention received. A user satisfaction survey is completed at Week 12 (after completion of physical therapy sessions) and again at Week 30 in both groups. This twelve-item survey has a total score range from zero to 24, with a higher number indicating greater satisfaction with the device.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
• Ankle dorsiflexion range of motion ≥ neutral when assessed concurrently with test stimulation in a sitting and standing position • Adequate ankle and knee stability during gait at the time of screening • ≥1 stroke of any etiology (eg, ischemic, hemorrhagic) experienced ≥ 3 months prior to study enrollment, as confirmed by independent medical records (if available) • Drop foot due to stroke sufficient to require use of an AFO • Adequate cognition and communication abilities demonstrated by either the participants scoring ≥ 24 (out of a possible 30) on the Mini Mental State Examination or having a competent caregiver • ≥18 years • Able to safely walk ≥ 10 m with a maximum of one person assisting • Self-selected (ie, comfortable) 10 m gait speed ≤ 0.80 m/second at the time of baseline assessment • Medically stable	• Fixed plantar flexion contracture ≥ 5 degrees in the hemiplegic leg with the knee extended • Excessive pain in the affected leg, as measured by a score ≥ 4 on a ten-point visual analog scale • Participating in any other interventional clinical studies without the sponsor's approval • Demand-type cardiac pacemaker, defibrillator, or any electrical or metallic implant • Significant swelling/edema in the leg extending up to the knee • History of chronic skin problems/conditions or cancerous lesion in close proximity to the expected site for FDS stimulation • Pregnant or plan on becoming pregnant • Botulinum toxin (type A or B) to the hemiplegic leg or arm within the past 6 weeks or planned during the course of the study • Expectation of a significant change in medications for spasticity • Unstable seizure disorder (average of ≥2 seizures per month) • Preexisting significant orthopedic conditions that would affect ambulation • Complete lower extremity hemisensory loss • Use of an FDS or other FES device for drop for an accumulative > 3 hours within the last 6 months prior to study enrollment • Major depression, as indicated by a score ≥ 10 on the Patient Health Questionnaire (PHQ-9), and not managed by a health care provider • Currently or planning on participating in a physical or occupational therapy program or new independent exercise program

Abbreviations: AFO, ankle foot orthosis; FDS, foot drop stimulation; FES, functional electrical stimulation.

A step activity monitor (StepWatch™; Orthocare Innovations, Oklahoma City, OK, USA) is worn for 7 days during Weeks 8 and 24 to quantify the amount of walking and to monitor compliance. Among the original control group, the step activity monitor is worn on both the nonparetic leg (to measure amount of walking) and the paretic leg (attached to the AFO to monitor compliance). Among the original treatment group, the step activity monitor is worn only on the nonparetic limb to measure amount of walking and the FDS is used to monitor compliance. The step activity monitor has been shown to be reliable, valid, and sensitive to changes in daily activity.[79–82]

Randomization

After baseline testing without the FDS/AFO, participants are randomly assigned by Bioness staff (JG) using an online program prepared by the study statistician (SW) in a process that is concealed by the site. Covariate adaptive randomization[83,84] is used to ensure balanced allocation at each site for age, time poststroke, and known confounders[85–88] within four subgroups: 3–6 months poststroke, >6 months poststroke, <65 years old, and ≥65 years old or a Medicare beneficiary. Persons > 6 months poststroke provide a more stable baseline "plateaued recovery state" and ≥65 years old or a Medicare beneficiary addresses the largest single insurance provider covering durable medical equipment following stroke.

Interventions

All participants, regardless of group assignment, undergo an AFO evaluation prior to randomization by an orthotist and physical therapist trained on "best practice points."[89] Although the intent of the study is to provide a comparison of the FDS with broadly-defined, standard-of-care "usual" AFO, a new AFO prescription is provided if indicated by the study team. The specific type of AFO (eg, solid ankle, hinged) prescribed for each participant is left to the discretion of the investigational staff. The orthotist and interventional physical therapist have undergone standardized training and onsite competency assessment.

Physical therapy intervention

During the first 6 weeks of the study, both groups receive eight sessions of physical therapy (twice a week for the first 2 weeks and once a week for the next 4 weeks). The original control group receives an additional 6 weeks (eight visits) of physical therapy after the 30-week crossover when they receive their FDS.

Table 2 Summary of outcome measures by time. Testing is performed with the subject using the device – foot drop stimulation or ankle foot orthosis – unless otherwise specified by "wo" (ie, without device)

Assessment	Baseline (V1)	V2 (Wk 0)	V3 (Wk 6)	V4 (Wk 12)	Wk 16	Wk 20	Wk 24	V8 (Wk 30)	Crossover visit[1]	V9 (Wk 36)	V10 (Wk 42)
Primary outcome											
10 m walk test (gait speed)	X (wo)	X	X	X				X (w, wo)	X	X	X
Secondary outcomes											
Timed Up and Go test	X (wo)	X	X	X				X (w, wo)	X	X	X
6-minute walk test	X (wo)	X	X	X				X (w, wo)	X	X	X
Berg Balance Scale	X (wo)	X	X	X				X (w, wo)	X	X	X
Functional Reach Test	X (wo)	X	X	X				X (w, wo)	X	X	X
Lower Extremity Fugl-Meyer[2]	X	X	X	X				X	X	X	X
Stroke Impact Scale[2]	X	X	X	X				X	X	X	X
Falls questionnaire[3]	X	X	X	X	X	X	X	X	X	X	X
Device satisfaction questionnaire[4]				X				X			X
Step activity monitor			X				X				

Notes: [1]Crossover visit tests only for the control group (starting with the crossover visit through to the end of study, the control group is tested using the FDS, ie, no longer tested with AFO); [2]always tested without the device; [3]also collected at each physical therapy visit; [4]performed for FDS and AFO, depending on group assignment (for the original control group, questions address the FDS after crossover).
Abbreviations: AFO, ankle foot orthosis; FDS, foot drop stimulation; Wk, Week; wo, testing occurs without device (FDS or AFO); V, outcome testing visit.

Treatment time for the first therapy session is 60 minutes, the second session 45 minutes, and the remaining six sessions range from 30–45 minutes. Regardless of randomization group, the first two to four therapy visits focus on education for use of AFO or FDS, initial gait training with the prescribed device, and the development of an individualized 30-minute home exercise program. During the remaining sessions, therapy includes gait training with the FDS or AFO addressing the primary limitations to safe and independent ambulation in the home and community as determined by the physical therapist's initial and ongoing assessments. Each physical therapy session includes a skin assessment. In addition, participants receive group specific education and therapeutic intervention as outlined below.

Original treatment group (FDS protocol)

Standard of care Bioness clinical protocols for the initial fitting, follow-up, home use, and conditioning of the FDS are used.[90] Education on the use and maintenance of the FDS is provided throughout the eight therapy visits. For the first 3 weeks, treatment participants follow the standard conditioning protocol that involves gradually increasing walking with the FDS from 15 minutes each day to all day use. The Bioness skin care guidelines[90] are reviewed and provided to the participant during the initial fitting. The first 3 weeks also involves using the FDS for cyclic stimulation ("training") when the participant is not walking. The goal of this training is to gradually strengthen and condition the muscles responsible for ankle dorsiflexion and eversion to avoid fatigue when using the FDS. Training is done 15 minutes two times daily for 1 week followed by 20 minutes two times daily over the next 2 weeks. An 8-hour break between training sessions minimizes fatigue and overuse.

Original control group (AFO protocol)

The control group is designed to maximize safety with the AFO and minimize bias (compared to the treatment group). Education on the use, care, and maintenance of the AFO is provided. An AFO wearing schedule is provided as needed (eg, new AFO). AFO instructions and skin care guidelines are provided and reviewed during the eight therapy visits. To reduce potential treatment bias, control participants receive surface sensory stimulation with a commercially available transcutaneous electrical nerve stimulation (TENS) device at each physical therapy visit, corresponding to the approximate time FDS is used in the treatment group. During the first week, participants receive 30 minutes of TENS at each physical therapy visit; during the next 2 weeks, they receive 30–45 minutes of TENS at each physical therapy visit. The TENS device is placed on the hemiplegic leg in a location that corresponds anatomically to the location where the treatment participants receive FDS stimulation. The TENS device is set to the lowest stimulation level that first yields a sensory response but no motor response. The settings for the TENS device include: continuous stimulation at a frequency

of 100 pulses/second, duration of 200 microseconds, and amplitude setting to elicit sensory response only. After receiving the FDS at the Week 30 crossover visit, the control group follows the FDS protocol outlined above.

Well visits

Well visit follow-ups performed at Weeks 16, 20, and 24 include a falls questionnaire and skin assessment. These visits also ensure participants are using the prescribed devices safely and appropriately between the outcome measure visits.

Sample size and power analysis

Recent studies suggest a standard deviation of 0.20 m/second for walking speed change from baseline to follow-up.[25,26,41] The original plan was to enroll 176 eligible participants (resulting in 132 with an estimated 25% drop out), allowing for 80% power to detect a clinically meaningful (0.1 m/second)[67] difference in walking speed change between groups using a two-sample *t*-test with a two-sided 0.05 level. After the first planned interim analysis (September 2011), the enrollment goal was increased to 206. As a result of favorable trends in outcomes for participants with severe gait impairment (<0.4 m/second gait speed), the hypothesis was added that among participants in this subgroup, those randomized to the FDS group would demonstrate greater improvement in gait speed than those randomized to the AFO group. This gait impairment category (<0.4 m/second) was chosen based on well-accepted categories of community ambulation[6] and previous research.[91–94] This increase in sample size allowed for: (1) the addition of a primary hypothesis for a subgroup of persons with initially severe gait impairment, and (2) to reduce the risk of type II errors on several secondary outcomes.

Statistical analysis

This study will test the primary hypotheses by comparing changes in outcomes from baseline to 30 weeks between treatment and control groups. The primary hypothesis is that participants using FDS will increase gait speed more than participants using an AFO, as measured by the total effect. This hypothesis will be examined in the entire group of participants, and also in the subgroup of persons with severe gait impairment (<0.4 m/second gait speed) at baseline. The following statistical approach will be taken to test the hypotheses.

First, demographic and baseline variables will be compared between the two randomly assigned groups using a *t*-test for comparison of means and chi-squared tests for comparison of proportions. Variables found to be significantly different between the groups will be used as covariates in the final analyses, in addition to prespecified covariates (site and prestudy AFO use).

Second, the primary intention-to-treat analysis will be performed at the 0.05 level. The study-wide error rate will be controlled by applying Hochberg's step-up procedure to two tests: one for the entire group and the other for the severe subgroup. Each statistical test will be based on Fisher's combination of two *P*-values: one from before and the other from after the first interim look. Both *P*-values will be derived from a linear regression model with walking speed improvement from baseline to 30 weeks as the dependent variable and the treatment group as the independent variable, controlling for prespecified covariates and pretreatment intergroup differences. For participants who do not complete the 30 weeks evaluation, their outcomes will be predicted by a fitted model that will take into account participant dropout bias.[95] More specifically, these three steps will be followed: (1) determine demographic and clinical variables that characterize differences between "completers" and "noncompleters;" (2) develop a model predicting outcomes for the "completers" using the significant independent variables from step one; (3) use the resulting model to predict outcomes for the "noncompleters," with the provision that for those who dropped out due to a related adverse event, their gait velocity changes will be imputed as the minimum of zero and the predicted changes.

If the above primary analysis is statistically significant, two subgroup analyses will be conducted using a one-sided two-sample *t*-test at the 0.05 level: one for those who are ≥65 years old or a Medicare beneficiary and the other for those who are ≥6 months poststroke. In addition, sensitivity analyses will be performed by comparing results from the intention-to-treat analyses described above. Also, the chi-squared test will be applied to compare the two randomized groups in the number of participants who move into new classes of clinically meaningful functional ambulation; participants will be divided into three categories: (1) who progress higher, (2) who do not change, and (3) who regress in their ambulation class status, eg, "household ambulators" (<0.4 m/second), "limited community ambulators" (0.4–0.8 m/second), and "full community ambulators" (>0.8 m/second).[6]

Third, Wilcoxon rank-sum tests will be conducted to compare secondary outcomes between the two groups. For simplicity, the "completers" only will be analyzed and there will be no adjustment for covariates. However, the familywise

error rate will be controlled at the 0.05 level for all secondary hypotheses testing based on Holm's step-down procedure, which rejects a hypothesis only if its *P*-value and each of the smaller *P*-values are less than their corresponding critical values.

In addition, a few tertiary analyses will be performed to compare the two randomized groups on trajectory of walking speed change and rate of falls, as well as a within-group test on whether the primary and secondary outcomes improved, diminished, or remained relatively stable from 30 weeks to 36 and 42 weeks.

Data management and quality

A secure web-based electronic data capture system (Rave®; Medidata Solutions Worldwide, New York, NY, USA) is used for clinical data collection and management. Third-party monitors perform regular visits at each site to review and verify all study data in source documents.

Study organization and management

The sponsor (Bioness Inc) is responsible for implementation of this protocol at each investigational site and ensuring that all data are collected in compliance with study protocol. They implement protocol changes, train study personnel, and oversee clinical/regulatory aspects of the trial in accordance with International Conference on Harmonization/Good Clinical Practice Guidelines and by Code of Federal Regulations Title 21. The sponsor also developed and maintains the manual of procedures, data collection forms, and the electronic database (Rave). With coordination from an independent publications committee, the sponsor will review and provide written consent prior to independent publications, presentations, or public disclosures. The sponsor will have no direct involvement in statistical analysis.

Discussion

This FASTEST multicenter randomized controlled trial is designed to compare the effectiveness of FDS to an AFO for management of drop foot in people with subacute and chronic stroke. The scope of this study is unparalleled in FDS research including: number of participants, number of sites, number of outcome measures, and the breadth of those measures across the entire International Classification of Functioning, Disability, and Health. There have been other FDS studies incorporating some of the design elements used in FASTEST, but not comparing standard of care (AFO), randomized, blind, and with an adequately powered sample size. Further, this study conducted six repeated measures over a 42-week period, allowing for investigation of longitudinal response and change.

Due to recent technology improvements, the use of FDS is increasing in the clinic, home, and community. However, AFOs are standard of care typically covered by third-party payors who consider FDS investigational. Previous studies comparing FDS and AFO have design limitations (eg, within-subject, cross-sectional designs). This is the first longitudinal, randomized controlled trial that compares FDS and AFO. Further, the trial will measure different aspects of change (immediate, training, therapeutic, and total as shown in Figure 1), thereby contributing significant information on the impact of FDS as compared to AFO not only as an orthotic but in its potential to facilitate therapeutic improvement in performance over time.

As stroke is a leading cause of disability in adults, evidenced-based intervention choices are critical to maximize potential in this large and growing patient population. Specifically, interventions that assist in restoring and improving walking ability can provide benefit beyond basic mobility and therefore the selection of a device or therapy targeting gait is critical as it can potentially influence overall quality of life. Even though foot drop has been identified as a major contributor of walking limitation in stroke, knowledge of the efficacy of devices is limited in the existing body of evidence. The results of this trial will provide a more comprehensive understanding of the impact of FDS and AFOs in the treatment of drop foot in persons with stroke and potentially serve to guide clinical decision making. The summation of the findings may serve as the definitive manuscript to date for the overall performance of FDS in select patients with stroke and its appropriate position in the rehabilitation continuum.

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