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Evaluating Foot-drop Interventions for Multiple Sclerosis Using a Multimodal System

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by

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Dedication

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Abbreviations	Definitions
AFO	Ankle-foot-orthosis
CAREN	Computer Assisted Rehabilitation ENvironment
CNS	Central Nervous System
DMT	Disease Modifying Therapy
FES	Functional Electrical Stimulation
GOAT	Gait Offline Analysis Toolkit
HBM	Human Body Model
IRB	Institutional Review Board
MS	Multiple Sclerosis
OM	Outcome Measure
PDDS	Patient Determined Disease Steps
PI	Primary Investigator
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
pwMS	Persons with Multiple Sclerosis
RPE	Ratings of Perceived Exertion
RRMS	Relapsing Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
USF	University of South Florida

Abstract

This dissertation explores how multimodal walking impacts quantitative and qualitative aspects of gait for persons with multiple sclerosis (pwMS) experiencing foot-drop. Foot-drop can dramatically impede mobility and clinicians routinely prescribe ankle-foot-orthosis (AFO) and functional electrical stimulation (FES) devices to alleviate its impacts on daily life. However, little is known about how these devices affect pwMS while traversing environments with real-world complexity. To explore this topic, an interventional, parallel assigned study was conducted. A realistic nature pathway containing changes in floor pitch, audiovisual stimulation, and during-trial tasks (for dual-tasking) was generated in an immersive virtual reality system called CAREN: Computer Assisted Rehabilitation ENvironment (Motek Medical, Netherlands). All participants wore a full-body set of 46 motion capture markers and had complete, passive control of their walking speeds. The primary outcome measures (OMs) of this study pertain to overall mobility and gait parameter symmetry. The secondary OMs are ratings of perceived exertion and confidence in walking ability. This study provides a normative cohort of thirteen participants aged 28 to 64 years; a case study of a pwMS, 58 years of age, who used two types of AFOs and an FES device; a cohort of three AFO-users aged 58 to 63 years, resulting in four AFO trials; a customized CAREN program that produces a realistic walking environment and collects full-body motion capture data; a detailed study protocol that can be modified for other populations, types of gait impediments, or types of interventions; anecdotal insights; and recommendations for future research.

Chapter 1: Introduction[i]

Multiple sclerosis (MS) is a progressive neurodegenerative disease that afflicts around 1-million people in the US and over 2.8-million worldwide.[1,2] MS is marked by the development of multiple neuronal lesions within the central nervous system (CNS). These lesions are caused by axon demyelination and scarring. MS typically develops in persons aged 20-50 years and afflicts women 2-3 times more than men.[3,4] MS is categorized into four types based on neuronal lesion progression rate: relapsing-remitting, primary progressive, progressive-relapsing, and secondary progressive.[5] MS symptoms and symptom severity change throughout the disease course and vary significantly from person to person. Symptoms are dependent on both the location and severity of CNS damage, and that damage is dependent on the individual's physiology, health, environment, and treatment history. Symptoms can range from minor visual, proprioceptive, or muscular control issues to complete loss of motor control, extreme proprioceptive deficiencies, and loss of higher cognitive functions like memory, analytical abilities, and mathematics skills.[6] Within the first 10 years of having MS, impaired mobility becomes the most visible clinical manifestation of the disease; it is also the primary contributor to disability.[7] Foot-drop syndrome is one of the most diagnosed symptoms of MS and directly affects both physical and psychological health by limiting

[i] Note to reader: Portions of this chapter have been previously published in Prosthetics and Orthotics International[23] and have been reproduced with permission from Wolters Kluwer. The reproduced portions are largely paraphrased, expanded upon, and tailored for this dissertation. The original publication contains information and insights beyond those cited in this dissertation.

mobility and independence. Although the exact prevalence of foot-drop in MS is unknown, about 85% of persons with MS (pwMS) report gait impairments as their primary concern, and that maintaining mobility is one of their highest priorities.[8,9,10,11]

Foot-drop is a condition in which a loss of motor control prevents the foot from adequately dorsiflexing. The dorsiflexor muscles generate the forces necessary to lift the toes upwards. They also work with their antagonist pair, the plantar flexors, to prevent contracture of the foot. Foot dorsiflexion provides the necessary ground clearance and proper heel-to-toe stepping required for stable walking during the swing phase of the gait cycle. If the toes cannot be lifted upwards enough, the individual may end up dragging their toes along the ground.[6] This increases their risks of tripping and falling, which are the two leading causes of serious injury for pwMS.[12] Compensatory motions are often employed to counter toe dragging, help maintain balance, and avoid trips and falls. Although these motions help in the short-term, they typically become exaggerated over time and cause muscular and joint damage in the lower limbs – which eventually affects the torso's muscles and joints. Examples of these motions include high stepping (lifting the knee higher than usual as if going up a stair), hip hiking (leaning to the side and lifting the hip as if attempting to straddle an object), and circular hip abduction.

Foot-drop can be countered with a variety of devices which fall into the following categories: noninvasive external (wearable) devices and invasive internal (implantable) devices. Although surgical, pharmacological, and physical therapy-based interventions can help with foot-drop, they are beyond the scope of this dissertation. This dissertation focuses on the two most prescribed and used wearable devices: non-actuated ankle-foot orthoses (AFOs) and functional electrical stimulation (FES) of the common peroneal nerve. These devices employ different methods to alleviate foot-drop, and each comes

with its own pros and cons for the wearer. Traditional AFOs are classified as passive (static) devices because they do not provide feedback or stimulation to the wearer to assist with motion. Their typically rigid construction simply supports and stabilizes the foot and ankle while preventing the foot from dropping below an approximately 90-degree position. Some worry that habitual reliance on AFOs can diminish muscular strength and conditioning to the point of atrophy,[13,14] but there is some evidence to the contrary.[15] AFOs are the standard treatment[16] because they are effective at addressing foot-drop, are inexpensive, and can be used in any weather condition. The major issues wearers have with AFOs are that they are typically bulky and aesthetically unpleasing, limit footwear and clothing options, become uncomfortable during use, develop odors over time, and make wearers self-conscious of their condition.[17] The author noted these AFO complaints during interviews with many pwMS (at a clinic, support groups, and study participants), neurologists who specialize in MS, and an orthotist. There is a variety of AFO designs and material compositions to choose from. Orthotists select appropriate AFOs based on the physical needs of the wearer. Traditionally, AFOs are made of plastic, but can also be metal, carbon fiber, or composite. The most common designs are rigid with shin heights customized to the wearer's needs. Less common designs are hinged at the ankle or actuated. Conversely, wearable FES devices are classified as active (dynamic) because they use transcutaneous electrical stimulation to activate the muscles responsible for dorsiflexion. The mechanics of FES devices help prevent muscle atrophy,[18-20] but persons with certain types of neuronal damage and skin sensitivities to adhesive electrode pads or transcutaneous stimulation cannot use these devices. Every FES device must be fit to its wearer by a specially trained orthotist. This orthotist will tune the device to deliver both comfortable and effective amounts of stimulation to the common peroneal nerve. The

biggest drawback of FES devices is their cost. They are expensive and usually not covered by insurance providers in the US for pwMS suffering from foot-drop. For reference in USD, the WalkAide currently costs around $4,500 while the Bioness L300 is around $6,000. Although MS-focused foundations in the US can provide financial assistance for purchasing an FES device, their grants are often limited and competitive. Other drawbacks of FES devices are that they cannot be used in water and require periodic maintenance and recalibration. Even with the financial barrier, FES devices rival traditional AFOs because they encourage muscle use, have sleek designs that make them easily hidden, and do not limit footwear or clothing options as much as AFOs.

Although AFO and FES interventions for foot-drop have been extensively studied for persons who suffered a stroke, stroke and MS have clear distinctions in their pathology, disease course, and demographics. Similar to stroke, research related to foot-drop resulting from traumatic brain injury or spinal cord injury are plentiful. Other neurological diseases (like Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis) can also cause foot-drop via brain atrophy and nerve damage; but, again, their demographics and disease courses are different from MS. Therefore, it is imperative that foot-drop interventions be discretely analyzed for each population.[21,22] The U.S. Food and Drug Administration (FDA) has approved AFO and FES interventions as safe and effective for pwMS, but the MS community still has many open questions about how they compare. It is unclear how their clinical and functional gait improvements compare given the user's level of disability, type of multiple sclerosis, walking environment, or desired physical activity. Device effects are often communicated as orthotic or therapeutic, and they differ based on the amount of time an intervention has been used. Both orthotic and therapeutic effects are reported as the difference between walking with and without the

use of an intervention. Orthotic effects refer to the short-term changes the wearer experiences and are either immediate or ongoing.[21] Immediate, or initial, orthotic effects are observed when the intervention is used for the first time.[21] Ongoing orthotic effects are observed over a period of time after regular intervention use.[21] Therapeutic, or training, effects refer to carry over from habitual, extended intervention use that remain when the intervention is ceased.[22]

1.1 Preparations for Designing the Research Study

The author conducted extensive literature reviews on MS, foot-drop, and foot-drop interventions; shadowed neurologists at the University of South Florida (USF) Morsani Medical Center's MS clinic for a few months; interviewed neurologists, pwMS, physical therapists, and an orthotist; attended several MS-specific lectures, seminars, and presentations hosted by clinicians; gained firsthand insights via observations and conversations with a close friend's journey with MS for more than 15 years; and published a systematic literature review on this topic with the journal Prosthetics & Orthotics International.[23] Each person on the doctoral committee was chosen because of their expertise and previous works related to MS, rehabilitation, engineering, statistics, gait and motion analyses, and/or disability.

1.2 Research Purpose, Goal, and Importance

The overarching purpose of this dissertation is to help pwMS who suffer from foot-drop lead the most active, independent lifestyles they desire. The focused research goal is to explore how multimodal walking impacts quantitative and qualitative aspects of gait for pwMS who use AFO or FES devices to treat foot-drop. Most gait studies examine device impacts within highly controlled environments where the flooring is level and predictable, audio and visual distractions are minimized, and the only task being

performed is walking itself. Although these studies provide crucial information, they only give an idealized snapshot of device effects. Real-world environments are much more complex and demanding. Many pwMS find traversing environments in their day-to-day lives difficult. This difficulty is furthered if they are engaged in other activities (dual-tasking), distracted by audiovisual stimuli, or suffering from foot-drop. In general, pwMS have elevated risks of tripping and falling, where trips and falls often result in serious injuries. Because of the challenges and elevated risks experienced while walking, pwMS typically reduce their levels of physical activity and socialization. These actions inadvertently lower both their quality of life and level of health. Although AFO and FES devices are the most prescribed methods of treating foot-drop, very little is known about how they affect pwMS during situations involving changes in floor pitch, dual-tasking, or audiovisual stimuli. This is unfortunate as real-world environments simultaneously contain all three. Understanding the impacts of AFO and FES devices within realistic situations will shed light on their day-to-day benefits for wearers. Clinicians can use this information to prescribe the most appropriate intervention for each patient's needs and improve their overall quality of life.

1.3 Overview of Study Design, Experimental Setup, and Outcomes

An interventional study was conducted using parallel assigned intervention and control groups. Intervention groups were split into two categories: AFO-users and FES-users. The author customized a program to create an immersive virtual reality environment using the CAREN system (Computer Assisted Rehabilitation Environment) (Motek Medical B.V., Netherlands). CAREN simulated a realistic nature pathway containing changes in floor pitch, audiovisual stimulation, and during-trial tasks (for dual-tasking). During the walking trials, participants passively controlled the treadmill's

speed in real-time via their location – allowing them to walk as naturally as possible. Data collected during trials included motion capture recordings of a set of 46 markers, ground reaction forces via force plates, qualitative questionnaires, and interviews. The primary outcome measures (OMs) of this study pertain to overall mobility, gait symmetry, and orthotic effects of foot-drop interventions. The secondary OMs are ratings of perceived exertion and confidence in walking ability.

1.4 Bulleted Research Summary

- The research goal was to explore how multimodal walking impacts quantitative and qualitative aspects of gait for pwMS who use AFO or FES devices to treat foot-drop.
- This study's design and environment are novel and were meticulously investigated and developed to produce a robust and targeted framework for achieving the research goal.
- This dissertation is novel and clinically relevant due to its unique design and exploration of a topic that is not well understood. Orthotists commonly prescribe AFO and FES devices to treat foot-drop in pwMS. Although both types of orthotics are safe and effective, they have almost exclusively been evaluated in highly controlled, clinical settings for pwMS. Little is known about their effects, individually and comparatively, during ambulation within environments containing real-world situations which are significantly more complex and demanding than those found within traditional clinical settings. Understanding device impacts on pwMS within environments similar to those they traverse daily, or ones they desire to traverse, will help clinicians prescribe the most appropriate intervention for each patient's needs.
- This dissertation provides the following original contributions to the field:
    - A customized CAREN program that produces a realistic walking environment and collects full-body motion capture and force plate data. Motek's Human Body

Model software was enabled for use with the 46-count full-body motion capture marker set; it runs calculations live and records .mox files for post-processing within Motek's gait analysis software. The multimodal environment has interactive functionality for dual-tasking and uses a self-paced mode that offers participants complete, passive control of treadmill speed and simulation progression rate, allowing them to walk as naturally as possible.

  - A robust study design and protocol that can be easily modified to evaluate other populations, gait impediments, or devices.
  - Analysis of normative cohort of thirteen participants aged 28 to 64 years.
  - A case study of a 58-year-old pwMS who used two types of AFOs and an FES device. Analysis was performed on four different walking trial conditions: no device, Ottobock's Walk-On Flex AFO, plastic hinged AFO, and WalkAide's FES.
  - Analysis of a cohort of three AFO-users aged 58 to 63 years, which included the case study participant. Analysis was performed on each participant's unaided walking trials and four different device trials: three used the Ottobock Walk-On Flex and on used a plastic, hinged AFO.

- The primary outcome measures (OMs) of this research are quantitative and related to overall mobility, gait symmetry, and orthotic gait. The secondary OMs are qualitative: ratings of perceived exertion and confidence in walking ability.
  - Mobility Parameters: walking speed, step width, step length, step time, stride time, stance time, swing time, cadence, and the percentage of time spent in the single and double support phases of ambulation.
  - Gait Symmetry Parameters: stance time, swing time, step length, step time, and the percentage of time spent in the stance, swing, and single support phases of gait.

Chapter 2: Background – Understanding Multiple Sclerosis

MS is a chronic, progressive autoimmune disease. The body attacks the neurons of the CNS, causing neuronal degradation that accrues and intensifies over time. The CNS is comprised of the brain and spinal cord, which controls most of the functionality of both the body and mind. Therefore, damage to the CNS can result in a vast range of symptoms that can be detrimental to performing tasks and interactions of daily life, which lowers independence and overall quality of life. The types and intensity of experienced symptoms depend on the location and extent of neuronal damage.

The equipment and techniques used to diagnose MS are well established, but there is a balancing act between time-to-diagnosis and accuracy of diagnosis. MRIs (magnetic resonance images) allow neurologists to detect the neuronal changes within the CNS that are indicative of MS. To definitively illustrate the progression of neuronal damage, a series of MRIs must be taken over the course of months, but the longer MS goes untreated, the more opportunities it has to damage neurons. The accuracy and speed of diagnosis are largely dependent on a clinic's available equipment and the neurologist's experience. Diagnosing MS quickly and early in the disease course is extremely beneficial for managing symptoms and slowing disease progression.

The origins of MS are not completely understood, and, currently, there is no cure for the disease or treatments capable of reversing neuronal damage. Therefore, efficiently slowing disease progression and managing symptoms to help pwMS maintain their current level of health is the best course of action. The majority of MS research and related

funding is focused on pharmacological treatments called disease modifying therapies (DMTs) and genetic projects that aim to identify the exact cause of MS and ways to regenerate damaged neurons.[23] A smaller subset of that research and funding is focused on assistive and rehabilitative devices and exercise, physical, and occupational therapies.

2.1 The Demographics and Epidemiology of Multiple Sclerosis

The number of pwMS is currently estimated to be around 1-million in the US and over 2.8-million worldwide.[1,2] Exact global and country-specific numbers are not available because of disease reporting regulations (or lack thereof) and the quantities of recorded data. Exact numbers are also limited, but to a lesser extent, by a country's ability to actually diagnose MS. In late 2018, the US CDC (Center for Disease Control) announced its plan to build and implement an MS registry through the National Neurological Conditions Surveillance System (NNCSS).[24] This surveillance system tracks case numbers and catalogs demographic information about pwMS. The NNCSS database is instrumental to helping clinicians and researchers better understand the disease and its epidemiologic trends and outcomes.[25] Other countries have similar registries and share their information so that global trends can be created and analyzed. Data collected and stored in these registries may include: age, race, ethnicity, sex, address, health care facility, date of MS onset/diagnosis, symptom onset/types, type of MS, DMT usage, cause of death, and prosthetic/orthopedic equipment prescribed by clinicians.[25]

In general, populations are reported and estimated in two ways: prevalence and incidence. Prevalence refers to the number of all new and existing disease cases over a designated point in time. Incidence refers only to the number of new disease cases. Additionally, prevalence and incidence can be communicated in two ways: as the total number of cases or as the number of cases per segment of the population. In the US, the

estimated prevalence of MS is nearly 1-million people (or 362 per 100,000), while the incidence is around 25,000 new cases every year.[1,2,26]

Typically, people between 20 and 50 years of age are diagnosed with MS, but it can develop in young children and those over age 60.[3] Women are 2-3 times more likely to develop MS than men.[4] The exact origin of MS is unknown, but researchers have identified four major factors that contribute to its development: genetic, environmental, immunological, and infectious.[27,28] Although these factors have been identified, their individual mechanisms and interactions with one another are not fully understood. MS is most common in persons with northern European ancestry; and geographical statistics has revealed that MS becomes more common in areas further away from the equator.[28] Although these ethnic and 'latitude gradient' statistics indicate genetic and environmental predispositions for MS, the data they are based on is incomplete. The extent of MS reporting is not equivalent across the globe; and many countries with economic challenges or political turmoil are more likely to lack reporting.

Although MS has a genetic factor, it is not necessarily an inheritable disease. The following statistics demonstrate the influence of genetics on MS development. They are from a 2012 publication,[4] so someone with access to the NNCSS may be able to generate better estimates now. Someone in the general US population has a 1 in 750 (or 0.13%) chance of developing MS. If someone has a parent, child, or sibling with MS, their chance increases to 2-5 in 100 (~3%). (It is unknown if the parent's gender affects the child's risk of developing MS.) Similarly, someone with a fraternal twin who has MS will have ~3% chance of developing MS themself. If someone has an identical twin with MS, their chance increases to 25-30%. Lastly, the chance of developing MS increases as the number of relatives with MS increases, but reliable percentages could not be found.

Environmental factors such as geographical location (specifically distance from the equator) and pollution levels are believed to hold significant influence on MS development, but they have not been confirmed as causing or worsening MS.[4] Many studies have illustrated that smoking tabaco not only increases the risk of developing MS, but also worsens symptom severity and quickens disease progression.[4] Insufficient vitamin D, especially early in life, negatively affects many systems of the body – most importantly the immune system. Because MS is an autoimmune disease, there is interest in determining if vitamin D levels can be used as a risk indicator for developing MS.

There are many infectious agents associated with increased risk of MS development; and exposure to them in early childhood is believed to have an even stronger link. To name a few: Epstein-Barr virus (EBV), measles, rubella, chicken pox, mumps, whooping cough, scarlet fever, and chlamydia pneumoniae.[4] EBV is a special consideration. It is called 'human herpesvirus 4' and represents one of the eight different virus types in the herpes family. It is one of the most common viruses among humans and can be symptomless. There is a high number of MS cases that have had EBV at some point in their life.[4] EBV causes infectious mononucleosis and other disorders. It incites the body to create high levels of immune antibodies to combat the virus. These antibodies are associated with the development of MS and neurologists often screen patients for EBV. Screening is especially important before prescription of DMTs because some DMTs produce deleterious effects in persons who had, or have, EBV.

2.2 The Pathogenesis of Multiple Sclerosis

MS is a chronic, progressive, immune-mediated disease. Although the exact cause of this disease is not fully understood, it is classified as an autoimmune disorder because the body mistakenly identifies its own healthy cells and tissues as foreign or hazardous. It

bombards those misidentified cells with both continuous and intermittently intense attacks to destroy and remove them from the body. In MS, these attacks are targeted at the myelin sheaths of the CNS's neurons. These autoimmune attacks stimulate an inflammatory response which mobilizes various cascades of leukocytes (white blood cells), plasma cells (white blood cells that make antibodies[ii]), macrophages (white blood cells that envelop and consume damaged, foreign, or hazardous substances), and healing exudates. This inflammatory response produces localized swelling and results in elevated fluidic pressure. This pressure can impede neuronal and cellular function and cause damage to those cells – which can assist in cell death and atrophy of brain tissue. Neuronal damage first occurs, and typically becomes the worst, near the veins that supply the CNS with blood. This implies a strong correlation between MS and the cardiovascular system, which further supports that it is an autoimmune disorder. The inflammatory cells linked with autoimmune diseases are circulated throughout the body via the vascular network and are transported to specific areas by passing through the vascular walls. In the case of MS, these cells pass through the blood-brain barrier[iii] (BBB) and travel outward into the highly vascularized regions of the brain and spinal cord.[5]

In MS, autoimmune attacks damage, and can completely destroy, the healthy myelin sheaths and oligodendrocytes[iv] of the neurons within the CNS through a process

[ii] Antibodies are proteins that trigger immune and inflammatory pathways which suppress, neutralize, or destroy cells, viruses, bacteria, and other foreign materials identified by the body as a threat. They identify these substances via antigens, which are substance specific markers that attach themselves to the threat's surface.

[iii] The BBB is a semipermeable membrane that separates the brain and the spinal cord from the rest of the body. It acts like a super filter by only allowing specific cells, nutrients, and waste to be transported across it.

[iv] Oligodendrocytes are the cells responsible for creating and maintaining the myelin sheath.

called demyelination. Myelin is a soft, insulating layer comprised of lipids and proteins which surround the axons[v] of neurons. This protective layer adds both flexibility and durability to an otherwise fragile structure. It shields the delicate axon from the fluidic environment of the body and aids the nerve fiber's ability to efficiently transmit signals. Once the myelin is removed, the axon is exposed to an array of environmental factors and direct attack from misguided inflammatory cells; both of which can damage and destroy the axon itself. When the myelin sheath is damaged, the neuron's ability to conduct signals becomes compromised. Although a neuron that experiences demyelination may not develop noticeable issues, the likelihood increases with accrued damage over time. The neuron's ability to conduct signals can be destroyed if the myelin sheath's damage is extreme enough or if the axon itself becomes heavily damaged or severed.

The autoimmune and inflammatory processes responsible for demyelination in MS typically come in intense waves that remove myelin unevenly and destroy some oligodendrocytes. The axons are left with patchy, gnarled myelin sheaths that the surviving oligodendrocytes try to repair; however, this process is imperfect. During the myelin regeneration process, plaques (also called lesions or scars) are created and make up part of the new sheath. This scar tissue, also called sclerosis, is hard and stiff as opposed to the soft, pliable myelin that was originally there. (This is similar to how muscular and dermal scarring differs from the original, highly plastic tissues that existed before extensive damage.) This new, sclerotic tissue hinders the neuron's functionality, but offers a degree of environmental protection it desperately needs. (A useful analogy for neurons and their myelin sheaths are electrical wires with plastic, isolative coverings. If

[v] Axons are the long, slender protrusions of neurons that conduct electrochemical signals from cell to cell.

the coverings are damaged or completely removed, the wires no longer perform as originally designed and the cores are exposed to potentially corrosive elements.)

The neuronal damage, and effects of that damage, may be completely unnoticeable for a single autoimmune attack, but MS is a chronic disease. MS usually presents a combination of a continuous, relatively mild autoimmune response with intermittent, intense attacks. Therefore, the myelin, oligodendrocytes, and neurons themselves are under a constant barrage of attacks and the damage they incur increases with the number and intensity of attacks experienced over time. As time progresses, the degree of sclerotic tissue rises, large groups of neurons lose their functionality, the body's ability to heal damage increasingly weakens, and the body finds it increasingly difficult, or impossible, to compensate for the disturbances in its neural network. These temporal changes result in clinical disease progression and the development and intensification of symptoms.

Neuronal damage of any kind is unhealthy, but the locations or clusters of neurons that become damaged have a huge impact on symptom development and intensity. When demyelination exposes the axons, it allows autoimmune processes to permanently damage the axons themselves. This permanent axonal damage creates permanent symptoms. There is a positive correlation between the degree of axonal damage and the severity of experienced disability. When damage is more limited to the myelin sheath, temporary symptoms that accompany acute autoimmune attacks are experienced. Although these symptoms can improve as the myelin sheath is repaired, the reparative process has its limits. Reparative abilities decrease with time as the degree of sclerotic tissue and death of oligodendrocytes increases. Therefore, even 'temporary' symptoms will begin to develop a baseline where they never truly disappear.

The degree of axonal damage that can occur with MS ranges from minor to extreme. Minor damage may not disrupt axon functionally appreciably or produce noticeable symptoms. Extreme damage can result in severance of the axon, which completely inhabits the neuron from conducting signals.[5] (This is analogous to having a highly corroded or severed electrical wire.) Over time, the degree of sclerosis and axonal damage results in debilitating symptoms that cannot be reversed – at least not with current medical knowledge. MS symptoms can decrease quality of life by limiting lifestyle choices and independence. Additionally, after axonal damage reaches a certain level, brain atrophy occurs, which creates new cognitive issues and symptoms.[5]

2.3 The Four Types of Multiple Sclerosis

MS is categorized into four distinct types which reflect specific patterns of disease progression: relapsing-remitting (RRMS), primary-progressive (PPMS), secondary-progressive (SPMS), and progressive-relapsing (PRMS). Each type is distinct in the way it progresses and affects the body. Some people can maintain very active and independent lifestyles with few signs of MS for most of their lives, while others quickly develop a level of disability that dramatically changes their lives. Although women aged 20-50 years are most commonly diagnosed with MS, diagnoses later in life tend to have worse prognoses, and men have a higher likelihood of developing more progressive forms of MS.[5]

2.3.1 Relapsing-remitting Multiple Sclerosis

Approximately 85% of pwMS have RRMS [29]. Persons with RRMS have unambiguous, acute attacks which last from 24 hours to weeks. These acute attacks – also referred to as exacerbations, flare-ups, or relapses – are followed by either full recovery or the experience of residual health deficits. (By definition, an exacerbation is associated with new damage and disease progression which must last at least 24 hours and occur at

least one month after the previous attack. Other 'attacks' are called pseudoexacerbations as they are unrelated to new damage from the disease. They are considered temporary aggravations of existing symptoms caused from elevated body temperature, infection, severe fatigue, or other stressors. Pseudoexacerbations vanish as soon as the stressor is remedied.) Periods of recovery and symptom stability are called remissions. Relapses can be obvious when new or worsened symptoms are experienced, but they can sometimes be quite minor. Relapse and remission periods correlate to the temporally changing levels of inflammation and neuronal damage. The time between attacks and degree of recovery are indicative of the body's health and degree of disease progression. Longer times between attacks, or more complete recoveries, are indicate that MS is not progressing significantly or quickly. Shorter times between attacks, or incomplete recoveries, are related to disease progression and worsened or increased varieties of symptoms.

2.3.2 Primary-progressive Multiple Sclerosis

Persons with PPMS experience a gradual progression of disability overtime, commonly without any relapses or remissions. However, some people with PPMS will experience periods of stable health and symptom severity, called plateaus or remissions. During plateaus, minor improvements in symptoms or degree of disability can be seen.

2.3.3 Secondary-progressive Multiple Sclerosis

This is a unique classification of MS. Someone is diagnosed with SPMS if their original RRMS transforms into PPMS. Essentially, the exacerbation periods increase in frequency, duration, and/or severity while the recovery periods decrease in duration and the degree of recovery lessens. Physicians cannot definitively predict who will develop SPMS, but there is a correlation between the degree of early neural damage and more

severe, long-term disability. Therefore, individuals with RRMS and significant neuronal damage have an elevated risk of developing PPMS.

2.3.4 Progressive-relapsing Multiple Sclerosis

This type of MS displays a clear progression of disability over time with the presence of acute relapses. Relapses may be accompanied by some degree of recovery, but typically this recovery is marginal at best.

2.4 The Prominent Symptoms of Multiple Sclerosis

MS can generate a wide array of symptoms due to the nature of the disease. Experienced symptoms depend on the location of neuronal damage within the CNS; and the severity of those symptoms depends on the extent of neuronal damage. There are several symptoms that most pwMS will experience to some degree in their lifetime. One of these symptoms is called foot-drop syndrome and is the primary focus of this dissertation. The following symptom discussions are limited to the most commonly experienced and those which influence foot-drop and mobility – which will assist with analysis and discussion of study participants.

2.4.1 Foot-drop Syndrome

Foot-drop can result from either muscular or neural damage and is experienced by many different populations and ages. In the case of MS, it originates from degradation of the neurons responsible for sending command signals to the foot dorsiflexors via the peroneal nerve system. The peroneal nerve system begins as an offshoot of the sciatic nerve within the deep tissue of the posterior thigh. The main offshoot is called the common peroneal nerve. It curves around the lateral side of the knee joint and branches into two smaller nerve bundles: the superficial fibular (peroneal) and deep fibular (peroneal) nerves. These two nerve branches travel down the anterior of the shank,

innervating various muscle groups along the way. They branch into even smaller bundles near the ankle and spread out to the dorsal and plantar regions of the foot.[30]

The common peroneal nerve passes command signals to the dorsiflexor muscles of the foot. If the transmitted signal is too weak or vanishes during transit, foot-drop results. The intensity of foot-drop can be a spectrum. At the lowest extreme, the person can still dorsiflex their foot, but this may require a lot more effort and the degree of flexion will be smaller than usual. At the highest extreme, the person is completely incapable of lifting their toes upwards to any extent. In the long term, this often results in spasticity and contracture of the foot and ankle. Contracture develops because the plantar flexor muscles are no longer balanced by their antagonist pair, the dorsiflexors. Foot contracture may result in the foot and toes being pulled into a pointed, often scrunched, position. Contracture not only inhibits proper range of motion and mobility, but it can also become quite painful. If the contracted muscles are not stretched and relieved, they can become permanently deformed and surgery may be required to help alleviate discomfort.

Moderate to extreme foot-drop dramatically affects mobility because the person is no longer able to adequately dorsiflex their foot during the swing phase of the gait cycle. This not only prevents them from being able to walk heel-to-toe for stability, but it can also force them to drag their toes along the ground.[6] Foot-drop is typically experienced on one side (unilateral), but some individuals develop bilateral foot-drop. Foot-drop increases the risks of trips and falls – the two leading causes of serious injury for pwMS.[12] The autoimmune nature of MS presents additional risks and challenges beyond just the physical trauma that directly results from a trip or fall. Because their immune systems are already being taxed, their healing capabilities are hindered; and they have elevated risks of developing opportunistic infections and diseases.

To counter the deleterious effects of foot-drop, compensatory motions are often employed – either consciously or subconsciously. They include high stepping, hip hiking, and circular hip abduction. In the short-term, these motions help the individual maintain balance and avoid trips and falls; but over time, they become an involuntary habit and produce damaging consequences. The altered gait patterns can become increasingly exaggerated with time as the muscle groups being engaged become more toned and dominant. The altered gait patterns and muscle groups produce abnormal stresses on other muscles, ligaments, and joints, which can lead to damage of those structures and increase the likelihood of injuries. Abnormal force loading will not stay localized to the lower limbs forever; eventually, issues will travel to the spine and upper body.

Dealing with foot-drop is both very physically and mentally demanding. Most pwMS will suffer from some level of fatigue, so the effects of foot-drop are particularly burdensome. Because neuronal damage is responsible for foot-drop in MS, physical and exercise therapies cannot cure this symptom. They are best suited for addressing muscular trauma and deconditioning that contribute to foot-drop. Currently, there are no technologies or treatments that can reverse or directly bypass the neuronal damage responsible for foot-drop in MS. The best course of action is to address the symptom and help maintain appropriate muscular tone and levels of physical activity. This dissertation focuses on the most prescribed, wearable devices that address foot-drop: AFOs and FES. One pharmaceutical can help pwMS improve their gait, Ampyra (dalfampridine), but it does not work for everyone and cannot be used in conjunction with some DMTs. Although the details of this drug will not be discussed at length as it is outside of the scope of this dissertation, dalfampridine was considered while designing the study protocols and interpreting results. Lastly, there are implantable devices and powered AFOs (which

verge on being exoskeletons) that are being developed as foot-drop interventions, but they are not fully FDA approved and are outside the scope of this dissertation.

2.4.2 Fatigue

Fatigue is both the most common and disabling symptom pwMS experience. For pwMS, fatigue is more than just being physically tired; the mental fatigue experienced has a huge influence on their daily lives and activities. In fact, fatigue is the number one reason pwMS leave the workforce.[6] It can affect anyone regardless of their MS type or how much time has passed since disease onset. MS-related fatigue is called lassitude: a state of physical or mental weakness, or lack of energy, that is overwhelming and seemingly unrelated to activity levels or time of day.[6] Fatigue can be caused by many different triggers. For some, rest or reduced activity levels helps; but for others, no amount of rest seems to alleviate the issue. There are some medications that can help address fatigue, but they cannot provide full relief. Below are the most prominent fatigue triggers for pwMS and ways in which they are commonly combatted.

- Temporary muscle fatigue can result from physical activity or repetitive movements. Simply resting may provide relief.
- Physical deconditioning from decreased activity and exercise levels can produce fatigue. Therefore, maintaining or increasing physical activities and exercise can reduce fatigue by benefitting the person's stamina, strength, flexibility, and cardiovascular health. Physical and occupational therapists often help pwMS develop appropriate and customized exercise routines.
- Neuromuscular fatigue is a unique symptom that accompanies neural degradation. As neuronal damage accrues, the individual must concentrate harder and expend more energy to perform tasks. Although some medications and maintaining physical

strength can help, they cannot fully combat this type of fatigue. Because neuromuscular fatigue stems from irreversible neural damage, the best way to alleviate it is by using assistive technology.

- Fatigue is a common side effect of many medications. Unfortunately, this includes many of the DMTs that are essential for slowing MS progression and the medications used to treat symptoms. If medication induced fatigue is disabling, clinicians will try alternate medications, use the lowest doses possible, or gradually increase the dosage – allowing for acclimation to the fatigue.
- Lastly, fatigue can result from the physical demands of just having an autoimmune disease, exposure to heat, disturbed sleep, and depression. Fatigue caused by MS itself can be addressed with some medications and use of assistive devices. Heat fatigue requires rest and cool environments for relief. Sleep and depression triggers can be remedied by addressing the sources of those ailments.

2.4.3 Cognitive Changes

Cognition refers to higher level brain functions that are responsible for comprehension, speech, visual perception and construction, analytics and mathematics, attention and information processing, memory, and executive functions like planning, problem-solving, and self-monitoring.[27] Cognitive changes may challenge someone's ability to understand or use language, recognize objects, navigate their body through space, focus, quickly process information, and even learn or recall information.[31] Cognitive changes in MS are linked with the person's lesion load and are rooted in the amount of permanent, axonal damage and atrophied brain tissue. Lesion load is based on the sum area of lesions within the brain, not just the degree of damage to a particular region.[6] Around 50-60% of pwMS will develop issues with memory, information

processing, and executive functions.[6] Cognitive changes progress slowly in MS and are typically mild, but some individuals experience changes that can be debilitating.

2.4.4 Muscular Spasticity and Contracture

Both spasticity and contracture interfere with movement and can cause discomfort and pain. Contracture occurs after prolonged spasticity. It results in abnormal or locked joint positions and is commonly seen in the hands and feet, but it can also develop in other major joints like the elbows and knees. Spasticity results from over- or under- stimulated muscle groups. For pwMS, as the CNS becomes damaged, it loses the ability to properly regulate the nerve impulses responsible for controlling muscle contraction and relaxation. Clinicians test for spasticity by performing reflex tests. If the patient's response to the applied stimulus is very small or non-existent, their nerves are being under-stimulated. If their response is abnormally high or abrupt, their nerves are being overstimulated. Spasticity produces an interesting correlation between limb movement speed and perceived stiffness: as an arm or leg is moved faster, it feels stiffer. Because of this, it is very difficult for someone with spasticity to perform fast, agile movements. They counter the spasticity by making movements more slowly, and as steadily, as possible. For highly active individuals, athletes, or persons whose livelihoods depend on being physical or dexterous, spasticity can be life altering. Mild levels of spasticity and contracture are treated with simple exercises and stretches that focus on the affected area's range of motion. If exercise therapy becomes ineffective, intense pain develops, or locomotion and the ability to perform tasks of daily living become severely inhibited, oral anti-spasticity medications, nerve blocks, surgeries, or subdermal devices can be prescribed.

2.4.5 Imbalance

The cerebellum helps coordinate body movements and is responsible for maintaining balance, equilibrium, and posture. There is a distinction between balance and equilibrium. Balance pertains to symmetric coordination between sides of the body. Equilibrium pertains to the perception of the body in space and maintaining orientation and position. No medications currently exist that can directly address imbalance caused by cerebellar damage, but some medications can help with equilibrium challenges like vertigo. If cerebellar damage is the cause of someone's imbalance, specific exercises can help them learn compensatory motions. Imbalance not only affects a person's physical safety, but it can force them to reduce their activities, change their lifestyles, and lose some degree of independence – all of which influence depression and quality of life. Assistive devices are prescribed if standing and walking become challenging or if the individual becomes prone to injury from imbalance-related falls. Canes, crutches, walkers, and braces are the most commonly prescribed devices. The chosen device depends on the needs and preferences of the end user as each one provides different user interfaces and degrees of assistance for maintaining balance.

2.4.6 Physical Weakness

Weakness induced by MS is similar to fatigue. Although physical deconditioning can contribute to weakness, it mostly stems from neuronal damage within the CNS. Maintaining good physical condition through regular exercise and activities will help with feelings of weakness, but it will not cure this symptom. Weakness and fatigue have a strong connection and impact on one another. Lessening the intensity of one symptom can help alleviate some of the impact of the other. Each pwMS has their own exercise or activity thresholds that they can withstand before experiencing fatigue and weakness. An

intense bout of fatigue or weakness can take some individuals days to recover from, so understanding their limits and developing appropriate goals is crucial. Either through personal exploration or guidance from a professional, pwMS can develop an exercise or activity routine that suits their needs and interests. Assistive devices can be crucial in helping pwMS complete activities that help maintain their levels of physical health.

2.4.7 Heat Sensitivity

Many pwMS develop a sensitivity to heat and become intolerant of performing activities (including walking) in warmer climates. Heat sensitivity can have a dramatic influence on other symptoms. It not only intensities fatigue, weakness, and spasticity, but also exacerbates visual disturbances, coordination issues, and challenges with cognitive functions. This leaves the individual mentally and physically drained and more prone to injury. Warmer environments also negatively impact sleep quality, which can influence many other symptoms as well. Thankfully, symptom exacerbation from heat is temporary and can be reduced by performing activities in cooler climates, out of direct sunlight, or in cool water; increasing breaks in activities for rest; and using items that can help lower or regulate internal body temperature (like cold beverages, cooling vests, and ice packs).

2.4.8 Visual Changes

In MS, altered vision can be caused by weakened optical muscles, damage to the optic nerve itself (via demyelination), or damage within regions of the brain responsible for visualizing and interpreting data from the eyes. Like many MS symptoms, the intensity of visual changes can be a spectrum, as are their impacts on daily life. There are many muscles around the eyes that control large motions (such as conscious translation of the eyes left, right, up, and down) and minute motions (such as subconscious rotational movements and tension adjustments for focusing and adjusting to changes in light).

When these muscles are weakened, it becomes difficult for the eyes to coordinate properly. This makes focusing and motion tracking tasks quite challenging. Eye incoordination often results in a condition called diplopia (double vision). Special prismatic eyeglasses can help reduce the degree of double vision, but they do not work for everyone. Diplopia can be treated with steroids, but they are a temporary solution. Another common condition caused by eye incoordination is nystagmus: painless, rapid, involuntary, and predominantly horizontal eye movement. Nystagmus can affect one or both eyes. Although this condition is easily identified by clinicians, the individual may not notice the rhythmic eye movement. If nystagmus becomes a hindrance to daily living, clinicians may prescribe Klonopin (clonazepam) to reduce its effects.

Visual changes originating from direct damage to the optic nerve or brain is permanent since the neuronal damage cannot be reversed. However, if these changes accompany a relapse or an acute autoimmune attack, they may improve during the remission period as the body heals and inflammation subsides. Lastly, optic neuritis may also result from direct neuronal damage. It is a temporary loss or disturbance of vision with potential pain behind the eye. Optical neuritis can create scotomas (blind spots) in the corners of the visual field.[6] Blurred vision and changes in perceived colors are also commonly experienced. Some corticosteroids, such as Solu-Medrol (methylprednisolone) and Decadron (dexamethasone), can help shorten episodes of optical neuritis.

2.4.9 Pain

Pain is split into two classifications for pwMS: primary (neurologic) pain and secondary pain. Neurologic pain results in dysesthesias, which manifests as sensations of burning, tinging, itching, and numbness. As the name suggests, neurological pain stems from neuronal damage which causes the nerve to misfire. Typical pain relievers will not

lesson the intensity of neurologic pain. A clinician must prescribe special medication that targets the nerve itself and alters the way it conducts signals. If medication or nerve blocks do not work, surgery can be used to physically sever the nerve which is causing the pain. Secondary pain, on the other hand, can be addressed with typical pain relievers. Secondary pain stems from physical sensations and other MS symptoms such as spasticity, contracture, and any number of physical injuries from trips and falls.

2.4.10 Osteoporosis

As humans age, the chance of developing osteoporosis increases. pwMS have an elevated risk of developing it as a 'secondary symptom' due to medications and DMTs, or as a byproduct of other symptoms – such as reduced mobility and physical activity. Osteoporosis changes the structure of bones and reduces their integrity. Bones that are weak, fragile, or brittle have a higher risk of breaking during a trip, fall, or unusual weight loading. As discussed previously, trips and falls are the leading causes of serious injury for pwMS, so acknowledging osteoporosis is important. pwMS work with their clinicians to keep track of hormonal changes and medications that may lead to osteoporosis. Maintaining mobility and regular performance of activities with weight bearing components are great ways to help combat osteoporosis and strengthen bones.

2.5 The Management and Treatment of Multiple Sclerosis

Neurologists who specialize in MS diagnose the disease, track disease progression, prescribe DMTs, prescribe treatments for specific symptoms, and provide referrals for other specialists as necessary. Treating MS and its symptoms can be complex. Treatment options depend on more than just the currently experienced symptoms and their severity. Before modifying or prescribing new treatments, pre-existing treatments, specifically

medications, and both current and past conditions must be considered. Although a treatment may help with one symptom, it can exacerbate or improve several others.

2.5.1 Disease Course Management

Modulating the immune response is currently the best way to treat MS. DMTs are used to slow down the demyelination of neurons by suppressing the immune system. Immune suppression is accomplished by lowering the overall count of white blood cells, usually by slowing or preventing their production. This helps reduce and prevent inflammation and the autoimmune response itself. In doing this, the current level of neuronal damage is maintained, and future degradation is slowed. Because pwMS already have compromised immune systems, treatments that suppress it further leave them more vulnerable to opportunistic diseases and harmful viruses and bacteria. The effectiveness of DMTs varies from person to person and over time as the disease progresses. Therefore, neurologists constantly re-evaluate prescribed DMTs and adjust them as necessary.

Prior to 1993, reliable methods of preventing autoimmune attacks or slowing disease progression in MS did not exist. Between 1993 and 2010, the FDA approved eight medications now used as DMTs: Betaseron (1993), Avonex (1996), Rebif (1998), Copxone (1996), Novantrone (2000), Tysabri (2006), Extravia (2009), and Gilenya (2010).[5,29,32] These medications are either injected, taken orally, or administered via intravenous infusion. Each one has its own set of benefits and side effects, but they all can reduce exacerbation frequency and lesion development – as detectable by MRIs.[29]

2.5.2 Symptom Management

There is a variety of pharmaceutical, physical, cognitive, assistive, and alternative treatments that pwMS use to manage their symptoms. No matter their classification, all of these methods share a common goal: maintain the individual's overall health and

current quality of life for as long as possible. Additionally, these different methods of symptom management are often used in conjunction with one another.

2.5.2.1 Pharmacological Treatments

Most MS symptoms have a pharmacological treatment option, but in-depth discussions of them are beyond the scope of this research. Clinicians carefully weigh the possible benefits and side effects of medications before prescribing them. Ampyra (dalfampridine) is of particular interest for this dissertation because it can assist with gait. It is a potassium channel blocker that influences neuronal signal conduction. Although dalfampridine can improve gait and walking speeds, it can induce or intensify other symptoms like vertigo, weakness, headaches, and imbalance. It was FDA approved in 2010 and remains the only medication that can positively influence gait for pwMS.

2.5.2.2 Physical Treatments

There are three major categories of treatments which focus on physical rehabilitation, health, and functionality: occupational therapy, physical therapy, and exercise therapy. All three share similarities in the symptoms they address and techniques they employ, but each has distinct goals. All three are commonly used to help pwMS suffering from foot-drop, fatigue, spasticity/contracture, imbalance, or weakness. Each therapy develops a customized routine based on the individual's needs, abilities, tolerances, and goals. The overall goal of occupational therapy is to improve the individual's ability to perform everyday tasks – specifically tasks related to independence and productivity in home or work settings. Tasks include dressing, personal hygiene, cooking, writing, driving, and operating electronic devices or machinery. An occupational therapist may also emphasize use of energy conservation methods to combat limitations related to cognition and sensory processing.[33] The overall goal of physical therapy is to

improve the individual's ability to perform movements, daily tasks, and activities safely – usually by addressing a physical injury, post-surgery recovery, or developed limitation. Physical therapists often help pwMS who are experiencing challenges with mobility, balance, posture, fatigue, and pain. If someone develops a permanent physical limitation, a physical therapist will help teach them safe and effective ways to compensate, including recommendations for assistive devices. Lastly, the goal of exercise therapy is to improve the physical health and functionality of a specific area of the body or the body as a whole. Exercise routines can be developed by the individual, a physical trainer, an occupational therapist, or a physical therapist. Exercise therapy is largely self-lead and self-monitored as it is completed at home or at a gym instead of a clinical setting with a certified therapist. Unfortunately, US insurance providers do not typically cover many occupational or physical therapy visits per year. pwMS who are able to visit a therapist are provided with recommendations for continuing treatment as self-lead exercise therapy.

2.5.2.3 Cognitive-based Treatments

Addressing the cognitive symptoms of MS is an interesting challenge. Cognitive rehabilitation specialists are contacted if issues with mental fatigue, memory, information processing, or executive functions begin to interfere with performance of daily tasks and work. Many techniques use repetitive activities to strengthen existing abilities; but if symptoms are permanent, emphasis is placed on learning compensatory strategies to help overcome experienced challenges. Therefore, cognitive rehabilitation is broken down into two main categories: restorative and compensatory.[31] Restorative cognitive rehabilitation aims to improve and restore someone's abilities. This is accomplished by performing repetitive mental exercises, where the goal is mastery of those exercises with gradual progression of difficulty. For example, memory and attention retraining involves

repetitive list-learning. Serial list learning requires the individual to sequentially recall patterns, numbers, facts, or other stimuli in the exact order they were presented. Compensatory cognitive rehabilitation focuses on teaching ways to counter permanent challenges to everyday activities. This type of rehabilitation focuses on organizational strategies, and ways to reduce distractions and increase focus and attention.[31] A common MS symptom that can interfere with cognitive function is mental fatigue, which the aforementioned treatments do not alleviate. If mental fatigue becomes inhibiting, the best course of action is to use energy conservation strategies. Energy conservation involves planning activities by evaluating current cognitive capacity versus the expected fatigue each activity may produce. In doing this, activities can be prioritized and spaced out as needed to allow for recovery.

2.5.2.4 Assistive Devices

A multitude of devices exist that assist with challenges related to mobility and performance of tasks in daily living and work. Because the focus of this dissertation is mobility, only orthotics and mobility aids are discussed. Both orthotics and mobility aids help with foot-drop, imbalance, spasticity, weakness, and fatigue. Orthotics are externally worn and provide support to improve stability and mobility. These devices commonly address postural and strength challenges caused by muscular or skeletal issues. Shoe inserts, AFOs, and FES devices are commonly prescribed orthotics for treatment of foot-drop. Mobility aids differ from orthotics in their design and method of interfacing with the user. They are not worn by, or secured to, the user; instead, the user holds onto or sits upon them. Mobility aids include walkers, canes, crutches, and wheelchairs, which are particularly useful for those suffering from imbalance. Trained service dogs can also be used to assist with mobility (particularly imbalance) and task performance.

Most mobility aids are readily available over-the-counter, but most orthotics require a prescription and appointment(s) with an orthotist. Orthotists are specialists who evaluate the physical abilities and needs of individuals, select an appropriate device, and customize the fit for both comfort and optimal functionality. Both orthotics and mobility aids are indispensable treatment options for pwMS. By improving the user's mobility and balance, they make ambulation safer and increase independence. They also enable their users to complete more exercises and activities, which improves their overall physical and psychological health.

2.5.2.5 Complementary and Alternative Treatments

There are many health-promoting strategies that are considered outside of the conventional realm of western medicine. Many of these complementary and alternative medicines (CAMs) have not been scientifically validated with controlled clinical trials or evaluated for placebo effects.[6] However, approximately two-thirds of pwMS in the US use some form of CAM, usually as a complementary medicine to their conventionally prescribed treatments.[6] Examples include specialty diets, vitamin supplements, herbal medicine, acupuncture, tai chi, ayurveda, and meditation. The potential benefits of some CAMs have generated so much interest that the National Institutes of Health (NIH) created a classification system for them.[34] In 1999, the US actually created a specialty branch of the NIH to evaluate CAMs: the National Center for Complementary and Alternative Medicine (NCCAM).

2.6 The State of Current Research[vi]

A systematic literature review was conducted to understand the current state, trends, and substantiated conclusions of foot-drop related MS research. The results guided this dissertation's study design, experimental protocol, and outcome measures. The systematic literature review had three main goals: (1) evaluate the state of AFO and FES research for pwMS, (2) identify the prevailing research trends, and (3) compare the clinical and functional effects these devices provide pwMS. Seventeen articles passed the eligibility criteria and were critically evaluated by a review team comprised of Laura Byrnes-Blanco, Kyle Reed, Rajiv Dubey, and Stephanie L. Carey. The lead author created a customized quality assessment form that the review team used to evaluate each article. The review process and customized assessment form followed the American Association of Orthotists and Prosthetists' (AAOP's) 12-step procedure for conducting a 'state-of-the-science evidence report.'[35] The Preferred Reporting Items for Systematic Reviews and Meta-Analysis was used for procedural comparisons and examples of figure designs.[36]

Three prominent research trends were identified while conducting the systematic literature review. These trends were based on the observations and results of the following processes: searching through multiple databases with specific key words and phrases, screening those search results one eligibility criterion at a time, and critically evaluating the publications that satisfied all of the eligibility criteria. First, only a small subset of MS-related literature focused on the evaluation or development of wearable, externally applied foot-drop devices on pwMS. Most of the research focused on pharmaceuticals,

[vi] Note to reader: Portions of this section have been previously published in Prosthetics and Orthotics International[23] and have been reproduced with permission from Wolters Kluwer. Only excerpts of this publication are discussed here for brevity. Please explore the full publication for additional, and more detailed, insights regarding the state of current research.

genetic therapies, or experimental wearable devices. Secondly, many publications did not actually focus on, or even use, pwMS. Many included pwMS as very small subsets of their sample population(s). If sample populations completely excluded pwMS, the study's results were extrapolated to them within the discussion and conclusion sections based on other literature. The third notable trend was that researchers used a diverse variety of testing environments, experimental protocols, outcome measures, and analysis methods. This produces both benefits and drawbacks. The main benefit is that concurring results are more robust if the supporting studies used diverse environments, protocols, and analyses. The main drawback is that the diversity of study characteristics can make direct comparisons or meta-analyses difficult, impossible, or misleading.

Some of the observed trends in MS literature may hinder the progression of foot-drop related MS research. Only five of the seventeen evaluated studies directly compared AFO and FES devices in their protocols; and only two of the seventeen studies used healthy controls. Controls and direct intervention comparisons are powerful tools for validating a study's testing environment, protocol, and results; and they are also essential for determining if studies can be compared head-to-head or combined for use in a meta-analysis. The MS community has open questions around the comparative effects of AFO and FES devices given the user's level of disability, type of MS, walking environment, or desired physical activity. Exploring and answering these questions requires unique, potentially novel, testing environments and protocols. Therefore, it is imperative that researchers validate their studies and make them as readily comparable to other studies as possible. This can be done by simply including control and AFO groups in their protocols and analyses – which provide normative baselines and comparator data, respectively. Publications should also collect and communicate thorough information

about participants and the devices used in their protocols. MS is a complicated disease, and many factors can influence performance and study results. Clearly communicating relevant information about participants is useful for results interpretation. Several of the evaluated studies omitted basic, yet critical, AFO information. Device information that should be provided are the manufacturer, model/design, and device material – all of which may influence gait and study results. Lastly, many of the evaluated studies correlated degree of device familiarity with general time of ownership. Although time of ownership is useful information, reporting the average frequency and duration of device usage is a better metric, especially when evaluating orthotic or therapeutic device effects.

The published systematic literature review presents a series of evidence statements comparing the clinical and functional effects AFO and FES devices provide pwMS. The publication summarizes these statements in a table, which groups them according to the intervention type(s) used within each study: AFO-only, FES-only, and AFO and FES. All studies that collected quantitative data conducted walking trials in controlled, clinical-like settings. Additional evidence statements are included in the publication, but the four most prominent, and well supported, evidence statements are: "(1) FES causes clinically and statistically significant increases in walking speed over both short- and long-term use; (2) FES not only causes clinically and statistically significant improvements in gait kinematics, but also produces more significant improvements than AFOs; (3) FES decreases perceived exertion significantly more than both AFOs and unaided walking; and (4) FES does not produce a training effect."[23]

Chapter 3: Study Design

An interventional study was conducted using parallel assigned intervention and control groups. It was approved by USF's Institutional Review Board (IRB). The IRB approved document, Pro#00040564, is provided in Appendix B. The lead author was the principal investigator (PI) for this study. Intervention groups were comprised solely of pwMS, who were split into two categories: AFO-users and FES-users. Following literature convention, AFO-users were considered the comparator arm and FES-users the experimental arm. This study was classified as an unblinded, open-label study since interventions were obvious. The original recruitment goal, which was primarily based on comparable publications, totaled thirty participants divided as follows: ten controls, ten AFO-users, and ten FES-users. This single-site study required participants to come to the USF Tampa campus for sessions, so realistic recruitment numbers were geographically restricted to Hillsborough County. To generate MS population statistics for the immediate area, the PI contacted the Multiple Sclerosis Division Director of Morsani, which is one of the most prominent MS clinics within Hillsborough County. Of Morsani's approximately 2,000 MS patients in 2021, around 200-300 presented with foot-drop, 40-50 persons used AFOs, and 15-25 persons used FES. Although insightful, these estimates did not guarantee that individuals could be reached, would be interested, or would satisfy the eligibility criteria. Table 3.1 summarizes this dissertation's study design.

3.1 Study Location, Collaborators, Sponsors, and Compensation

This single-site study was conducted at USF's Research Park within the Interdisciplinary Research Building. Neurologists at the USF Morsani Medical Center assisted with recruitment. This study was not funded or sponsored by any organizations, companies, or grants. All participants and study personnel were unpaid volunteers.

3.2 Recruitment Strategy

Participants were recruited through a combination of neurologists at the USF Morsani Medical Center, outreach with local MS support groups and organizations, and word-of-mouth. All interested persons directly contacted the PI to receive additional study information and a link to the digital study application form (Appendix C).

Table 3.1: Study Design Summary

Study Details	Choice
Study Type	Interventional Study
Number of Groups	Three (AFO-users, FES-users, healthy controls)
Intervention Model	Parallel Assignment
Masking	Open Label (Unblinded)
Primary Purpose	Treatment Evaluation
Disease of Focus	Multiple Sclerosis
Condition of Focus	Foot-drop Syndrome
Clinical Trial Phase	Not Applicable
Experimental Arm	Functional electrical stimulation: WalkAide and Bioness L300
Active Comparator Arm	Ankle-foot-orthoses
Recruitment Total*	30 (ten AFO-users, ten FES-users, and ten controls)

*These were the original recruitment goals.

3.3 Foot-drop Intervention Requirements

Only pwMS used foot-drop interventions during walking trials. They were required to bring and operate their personal device, which had to be orthotist prescribed and FDA approved. This ensured that wearers had appropriate interventions and understood how to use and care for them. FES devices were restricted to the WalkAide (Innovative Neurotronics, Austin, TX) and the Bioness L300 (Bioness Inc., US). No manufacturer or style restrictions were placed on AFOs because of the wide variety of FDA approved options. No modifications were made to devices and participants were instructed to use them as usual.

3.4 Eligibility Criteria

Table 3.2 lists the eligibility criteria used to screen participants. They are grouped into inclusion and exclusion criteria for controls and pwMS. They were carefully selected to ensure that participants could safely complete the study, and that the study's sample MS population would be representative of the target MS population. Since this study was not funded and used a novel and physically demanding testing environment, it was necessary for these criteria to be stricter than comparable publications. Many MS-related publications use too lax of criteria,[23] so these stricter criteria both address that issue and help provide more robust information about participants. Information required for sample population demographics, data analysis, results interpretation, and overall study transparency were collected via the study application form (which was used to determine eligibility) and the participant data sheet (Appendix D).

Table 3.2: Eligibility Criteria

<table>
<tr><th></th><th>AFO-users and FES-users</th><th>Controls</th></tr>
<tr><td>Inclusion Criteria</td><td>• Have clinically diagnosed multiple sclerosis.
• Exhibit unilateral foot-drop which interferes with mobility and alters gait biomechanics.
• Regularly use either an AFO, WalkAide, or L300 device for a minimum of 30 days.
• Have a PDDS* score between 3 (gait disability) and 5 (late cane).
• Be between 18 and 75 years of age.
• Be able to ambulate a minimum of 50 meters without stopping and without the use of an assistive device (i.e., a cane, walker, or crutch).
• Have the cognitive capacity to do the following without assistance:
- Understand and follow study protocol.
- Give consent.
• Have used a consistent dosage of AMPYRA (dalfampridine), if used, for at least 30 days.
• Not be a prisoner or have a warrant, parole, or felony.</td><td>• Be free of injuries or medical conditions that affect gait or the cardiovascular system.
• Be between 18 and 75 years of age.
• Be able to ambulate a minimum of 50 meters without stopping.
• Have the cognitive capacity to do the following without assistance:
- Understand and follow study protocol.
- Give consent.
• Not be a prisoner or have a warrant, parole, or felony.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="2">The following applies for all participants:
• Have any of the following health issues that may interfere with ambulation:
- Congestive heart failure.
- Cardiopulmonary disease.
- Uncontrolled diabetes.
- Joint or bone problems that limit movement, i.e., arthritis or healing bone fractures.
- Pressure sores or open wounds on legs.
- Muscular damage that is still healing.
- Active cancer treatment.
- Chronic alcohol abuse.
• Currently participating in another study or clinical trial.
• Have a history of epilepsy or seizures.
• Be pregnant.
• Experienced a physical injury within three weeks of beginning the study.
• Be a prisoner or have a warrant, parole, or felony.</td></tr>
</table>

*PDDS stands for 'Patient-determined Disease Steps' and is determined via Appendix E.

Chapter 4: Experimental Setup and Quantitative Data Acquisition

The majority of gait studies are conducted in clinical settings where the flooring is flat and predictable, audiovisual distractions are minimized, and the only task being performed is walking.[23] These idealistic walking environments provide useful information, but they are not representative of the environments encountered in everyday life. Real-world environments contain a multitude of audiovisual distractions and changes in floor pitch; moreover, people are typically engaged in multiple activities as they walk. Therefore, understanding how foot-drop interventions impact pwMS in their daily lives requires more complex approaches than those commonly used for gait studies.

Quantitatively analyzing gait parameters within realistic, everyday environments is a challenging task. The testing scenario must be complex enough to produce a realistic walking environment, highly controllable for repeatability from session to session, and equipped with technologies that can record a variety of data continuously. The biggest inhibitors for these environments are the cost and time required for their development, management, and operation. Few publications have conducted such complex studies, and this dissertation is among the first to focus on pwMS.[23] The goal of this research is to explore how multimodal walking, as encountered in everyday life, impacts pwMS who use AFO and FES foot-drop interventions. To accomplish this, the author used an immersive virtual reality system to produce the testing environment and collect quantitative motion capture data. The utilized virtual reality system is called CAREN – short for 'Computer Assisted Rehabilitation ENvironment' (Motek Medical B.V., Netherlands). CAREN was

designed for clinical, hospital, and research markets that focus on rehabilitative solutions.[37] The author used CAREN to generate a nature pathway containing audiovisual distractions, changes in floor pitch, and during trial tasks for dual-tasking. It produced a highly controlled, highly repeatable testing environment with high resolution motion capture, force plate, and video camera recording capabilities. CAREN is integrated with a Vicon Nexus motion capture system (Vicon Motion Systems Ltd, UK), which collects and transmits all the raw motion capture and force plate data required for CAREN's operation.

CAREN consists of a series of systems that are integrated and controlled with D-Flow programs, called 'applications.' The author customized a D-Flow program to satisfy her experimental setup and data acquisition needs. The resulting program is unique due to its complexity and functionality. An important feature the author enabled is a self-paced mode for walking on CAREN's treadmill. This mode allows participants to have full control of both the treadmill's speed and the simulated pathway's progression rate. In this mode, the system responds to the participant's location on the platform – making control a completely passive process. This allows participants to move as naturally as possible and results in a realistic walking experience. This unique testing setup allows quantitative information to be collected that would be extremely difficult or impossible otherwise. Raw data recorded within the customized D-Flow program includes continuous force plate readings, XYZ coordinates of all 46 motion capture markers used, treadmill speeds, treadmill pitch, and number of targets hit and missed. It also records the .mox files required for post-processing data within Motek's Gait-Offline Analysis Toolkit (GOAT) – which outputs several useful parameters for analyzing and interpreting gait. In the end, the recorded information provides an uncommonly complete data set that can be used to test a wide variety of outcome measures.

4.1 Vicon Nexus and Motek's Data Analysis Software

Vicon Nexus version 2.8.1 was used for this study. The system consisted of ten motion capture cameras: nine were Bonita 10's and one was a Vero v2.2. All cameras were secured to a metal frame that surrounded the CAREN's motion platform – providing a large 360° capture volume. All default camera and system settings were used for calibration and data recording. Although data from CAREN's imbedded force plates could be accessed and recorded within Nexus, all their settings were locked by Motek. Therefore, the default force plate settings were used, and force plate calibrations were completed within the D-Flow program itself.

Motek has two primary software programs to analyze motion: (1) the Human Body Model (HBM) and (2) GOAT. These software packages are only compatible with Motek's specialized marker sets – one being a lower-body set and the other a full-body. Because of this, Motek provides the necessary marker template files required for calibrations within Nexus and D-Flow. The author used Motek's provided full-body marker template file to calibrate within Nexus: 'FullBody_HBM2.vst.' Although this file contained all the correct marker designations, it contained improperly designated body segments within the torso and upper limbs. This meant that Nexus could not properly complete static and dynamic skeletal calibration operations related to the torso and upper limbs. Most notably, it consistently placed the neck and head segments within the torso when these two calibration operations were performed. This did not impede CAREN operations, interfere with recording raw data, or affect this study's gait analysis. However, this error limited the processing capabilities of HBM and GOAT to only lower body parameters. It also made post-processing data with other Vicon software infeasible because they require fully processed data files for operation.

Although Vicon provides guides for several marker sets commonly used in industry, they do not provide specifics on to how to modify or use Motek's proprietary marker sets with their software. HBM and GOAT analyses are dependent on both the marker and segment designations produced by Nexus. Because Motek's provided .vst file contained the correct marker and lower body segment information demanded by Nexus, HBM and GOAT could produce the lower body kinematics and gait parameters this study required. Again, the torso and upper body kinematics were not essential for analyzing gait, but this study's raw data could be used to calculate those kinematics via other methods or after re-processing with a corrected .vst file.

4.2 CAREN System Components

A collection of integrated software and hardware comprise the CAREN system: HBM, GOAT, a large 180° projection screen, three projectors which produce illusion of depth, the Vicon Nexus system outlined above, surround sound speakers with subwoofer, a six-degree-of-freedom motion platform, Motek ForceLink split belt treadmill with integrated left and right force plates (which are imbedded into the platform), and three black-and-white video cameras. For safety, handrails and a harness suspension frame were rigidly affixed to the platform, a full-body harness was used by all participants, and an electric bridge with handrails was used to walk participants and study personnel on and off the system. The bridge was necessary to traverse the depression of the building's foundation that was required to accommodate the motion platform's electronic and hardware components and allow the platform to have maximal range of motion. All CAREN-related equipment was maintained by Motek via USF's maintenance contract with them. No modifications were made to CAREN's system components, and all system settings were kept at their defaults for calibration and data recording.

4.3 The Original D-Flow Program and Multimodal Walking Environment

D-Flow version 3.34.0 was used for this study. It is a proprietary visual programming language developed by Motek. D-Flow is used to integrate and control all of CAREN's systems for operation, data recording, and processing data with HBM. The author meticulously explored each D-Flow program Motek provided as part of their standard application package and within their example projects folder. Searching for programs with features that closely matched this study's specifications and learning how Motek used D-Flow to control various functions was the best method to produce a customized D-Flow program. Although many programs were available, only the four standard applications came with quick-start guides. The rest of the programs lacked directions, descriptions, or within code comments for their purpose or operation. Combined with the lack of a CAREN-user forum or an advanced programming guide, understanding the ins-and-outs of D-Flow took some time.

After receiving the 3.34.0 updates in early 2021, the author located a suitable program within the example projects folder that could be used as a starting point. It not only addressed most of the programming issues found in the older standard road application, but its programming was also more streamlined. This new forest road application presented the foundational requirements desired for the author's multimodal walking environment (changes in floor pitch, audiovisual distractions, and during-trial tasks) and was capable of using the self-paced mode. This program simulated a nature trail that started within and traveled through the woods and terminated at a wooden shelter overlooking a mountain bluff. It provided visual distractions via scenery changes as the simulation progressed. Scenery included trees, clouds, grass, stones, bushes, and far-off hills. Auditory distractions were achieved by playing ambient bird and cricket

sounds throughout the simulation. The nature trail's pitch could be perfectly flat or include incredibly steep hills depending on the 'scene scaling' chosen from a dropdown menu. All non-flat pitch settings had hardcoded locations along the length of the trail where hills occurred. Each hill's accent and descent profile used hardcoded scaling factors linked to the scene scale chosen from the dropdown menu. Dual-tasking was achieved by enabling 'encounters' where participants are tasked with swatting away oncoming targets. When encounters are enabled, two things happen: (1) two semi-opaque spheres appear on the screen and (2) a series of butterflies and birds (e.g., targets) fly down the trail towards the participant over the course of the entire trail. The spheres are connected to participants' hands so that their left hand controls the left sphere, and their right hand controls the right sphere. The size of the spheres can be selected from a dropdown menu. Smaller spheres increase task difficulty as the surface area available to collide with targets decreases. Each butterfly and bird had a unique, pre-programmed flight path containing changes in speed and multiple changes in direction. When a sphere overlaid with the body of a target, it counted as a collision and the target flew off the screen. During collisions, a red outline encircled the target and a 'bwooop' noise was sounded to indicate that a collision was successful. This during-trial task provided additional audiovisual distractions and tested the participant's focus, dexterity, balance, and cognitive capabilities. The targets' sizes and flightpaths were hardcoded into the program and could not be customized. Table 4.1 lists the dropdown menu options related to pitch and encounters. The author carefully evaluated and selected each setting to ensure that the walking trials would be achievable, yet challenging, for someone with foot-drop. A sphere size of '3' and pitch intensity of '2' were chosen for this study. They resulted in sphere diameters slightly larger than the targets' torsos and made the largest hill's pitch

comparable to the slope of a low, 2.8% grade driveway. Figure 4.1 illustrates the platform's pitch profile along the approximately 215-meter-long trail. Figure 4.2 shows a snapshot of the nature trail graphics with a scene scale of '0' – one sphere is visible in this image as they overlap until the program is calibrated to the participant's hands. When other scene settings are chosen, the cobblestone pathway visuals are scaled for each hill as they are approached and traversed – providing the illusion of inclines and declines.

Table 4.1: Nature Trail Setting Options

Sphere Size Options ('Encounter Level')	Pitch Intensity Options ('Scene Scaling')
0 – no encounters	0 – flat
1 – small	1 – low
2	2
3 – medium	3 – moderate
4	4
5 – large	5 – extreme

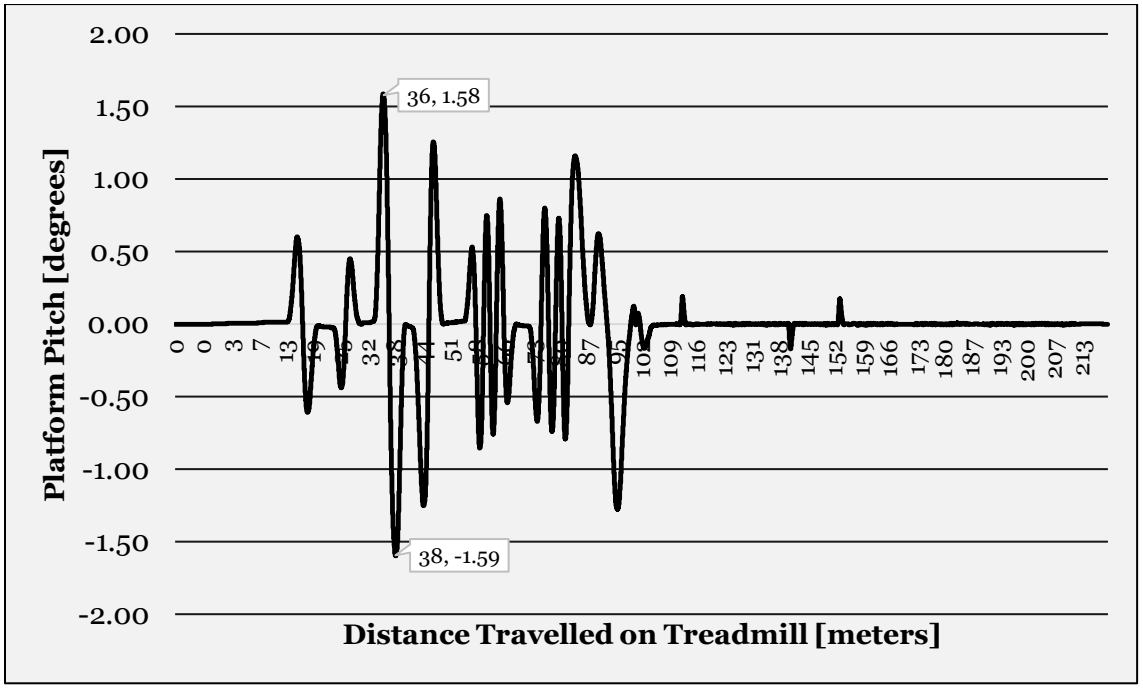

Figure 4.1: Pitch Profile of Motion Platform vs Distance Travelled

Figure 4.2: Nature Trail with Zero-degree Pitch

4.4 Customization of the D-Flow Program

Although the program discussed above could produce all of the foundations for a multimodal walking environment, its usefulness for this study was very limited. It required several additions and modifications to satisfy this dissertation's requirements. The final, customized program is titled "07_LBB_MS_dissertation" and consists of the following three file types that are required to operate the CAREN system: .caren, .dflow, and .screenconfig. It operates with Motek's 2020 full-body marker set, records a variety of raw data required for analysis, runs the HBM program in real-time and records outputs from it, and records the .mox files required by GOAT for creating gait reports. The original program was not designed for any of those tasks. Program alterations also made the simulation more immersive for and responsive to participants, streamlined data recording, and provided participants with audiovisual cues for when they should begin

and stop walking. Customizing the program was a long and tedious task. Each module within the program had to be evaluated individually and in conjunction with all of the other modules and global events, which trigger various actions. Every module has its own settings, links to global events, and can contain multiple menu tabs. Some have sections for codes or equations to manipulate incoming or outgoing information, and some import codes or files for operation. Additionally, almost every module has multiple connections, with sub-connections, to other modules. Figure 4.3 shows the overall module layout in the customized D-Flow program. The author added titles and descriptions to most of the individual modules and module groups to clarify their purposes.

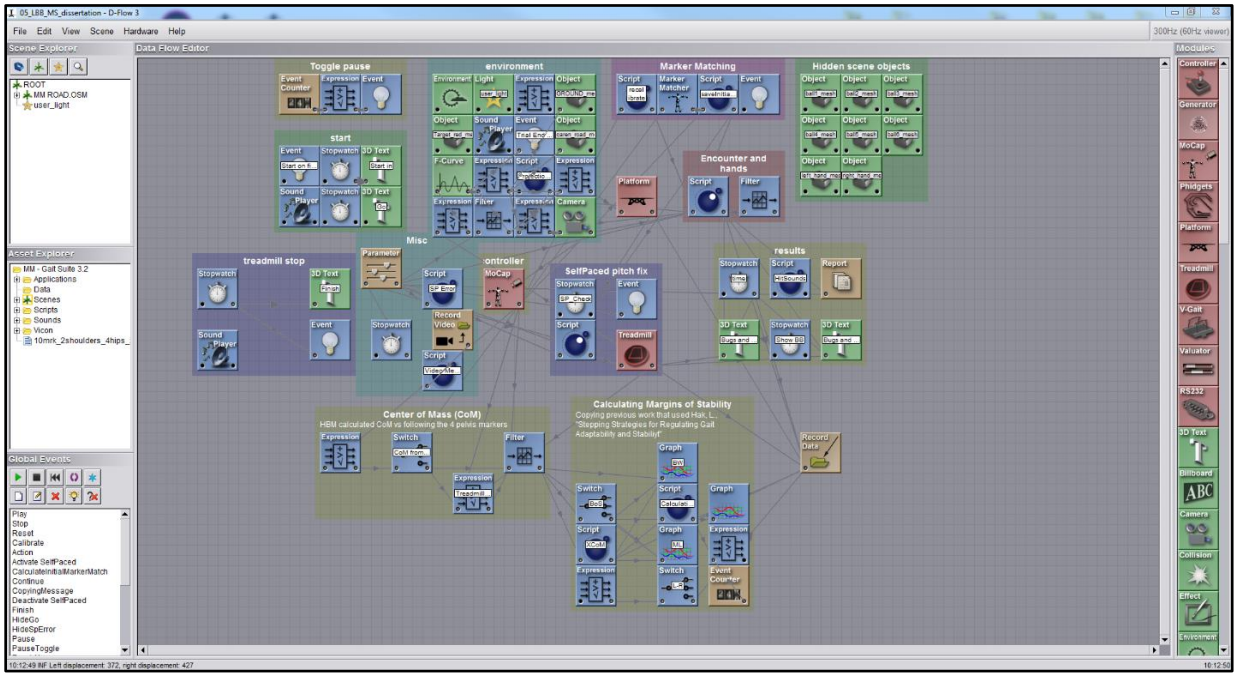

Figure 4.3: Customized D-Flow Program

The original program was insufficient for this study because it was predominantly hardcoded and designed to operate with an unlabeled set of six markers: RFIN, LFIN, LASIS, RASIS, LIPSIS, and IPSIS. Information on these marker labels and the entire

2020 full-body marker set are contained in Appendix F. Although designating markers as 'unlabeled' eliminated the need to calibrate participants in Nexus, it prevents HBM from operating and the .mox files required by GOAT from recording. Furthermore, HBM and GOAT can only operate with Motek's full- or lower-body marker sets. Because the full-body set provided opportunities for analysis and visualization of participants' entire bodies (which is more unique and versatile for future research and meta-analysis), it was chosen over the lower-body set. Customizing the program required meticulous work, so only the most impactful modifications are topically discussed below.

- Automatic display of a transitional '3-2-1-GO!' countdown in large, green text at the start of the trail to accompany the pre-existing green light indicators and beeps.
- Automatic display of the following in large, red text during the last few meters of the trail near the shelter: 'Treadmill will stop in: 6-5-4-3-2-1.' The six-second countdown is accompanied by a series of longer and lower toned beeps than were used at the program's start. The original program did not provide any warnings or indications to stop walking; it just suddenly hard-stopped the treadmill once the shelter was reached.
- Addition of individual module and module group titles with accompanying descriptions to better track their purposes and settings within the program. The original program had sparse information and next to nothing for comments.
- Connection of the Record module to global commands. Recording starts automatically when the program's 'play' button is clicked and continues to record until the 'stop' button is clicked. This Record module creates a column delimited text file that pulls in data from several other modules. Descriptive labels are included for each column of data. The variety of recorded data was chosen out of both necessity and prudence: timestamp; the position, rotation, and speed of the platform along the x, y, and z axes;

the speed of and distance travelled by the left and right treadmill belts; treadmill pitch; elapsed time since the start button was clicked; number of encounters hit and missed; total percentage of hits for the trial; the participant's extrapolated center of mass (XCoM) along the x, y, and z axes; the margin of stability (MoS) along the x (medial-lateral) and z (anterior-posterior) axes; the force, moment, and center of pressure on the left and right force plates along the x, y, and z axes; and the participant's center of mass as calculated by HBM along the x, y, and z axes. Although the original program contained a Record module, it was not setup to start or stop recording automatically, and it only recorded a few basic parameters.

    - The module groups and Lua scripts related to XCoM and MoS are included but deactivated within the final program. The author found them within other Motek programs, but they contained errors and hardcoding that inhibited their full incorporation into the customized program. Because XCoM and MoS did not need to be calculated in real time and the CAREN system was already being taxed by this program, the author deemed calculating them via post-processing a better method.

- Deletion of the original program's parameter displays. The original program would continuously display the participant's walking speed, distance traveled, and number of targets hit and missed. They detracted from simulation immersion and inhibited natural walking behaviors, so their removal was necessary.
- Configuration and activation of HBM in the MoCap module for the full-body marker set. This entailed selecting and specifying several parameters across a few menu tabs. These included: importing live, labeled marker data directly from Nexus; specifying that imported data contains 46 markers and 22 segments; enabling .mox and video

files to be recorded; directing HBM to process gait data in real-time; and ensuring all of HBM's parameters were clearly designated and recorded as outputs.

- Modification of triggers and creation of global events to automate audiovisual instructions and to streamline data recording.
- Alteration of treadmill settings within the Treadmill module to improve immersion for and responsiveness to participants. The three main changes were:
    - Linking the left and right treadmills so they moved in unison. This created a large, homogeneous walking surface for participants.
    - Increasing the treadmill's top speed and acceleration/deceleration limits. This improved treadmill responsiveness while using the self-paced mode. The original limits resulted in notable motion delays which hindered natural gait.
    - Disabling the default 'treadmill stop' commands. In the original program, if participants walked too slowly or stopped momentarily, the treadmills and simulation progression would hard-stop and remain locked until the trial was restarted. This not only destroyed immersion, but also interrupted data recordings and complicated data analysis. Disabling these default settings made the final program's self-paced mode more realistic by allowing participants to slow down, completely stop, and continue walking at will. The system simply responds in kind and all data recordings remain uninterrupted.
- Creation and implementation of a 2020 full-body marker template for use with the Marker Matcher module. In this program, the Marker Matcher module distinguishes and tracks the location of all used markers; then it feeds specific marker coordinates to the modules responsible for the self-paced mode and sphere control functions. The Marker Matcher module uses an example template to calibrate to participants. This

template must list the number of markers present and contain the titles and ZYX coordinates of all those markers. The original program was hardcoded to operate with the limited, unlabeled six-marker set. It frequently lost track of and swapped markers during live trials. This not only hindered the responsiveness of the self-paced mode, but also resulted in participants losing control of the spheres. Periodically losing control of the spheres, even for a couple of seconds at a time, is enough to frustrate participants and affect their gait. Activating HBM with the labeled, full-body marker set caused errors with the original Marker Matcher module since its template must exactly match the markers being used on participants. Motek's provided selection of marker templates was limited and none of them were compatible with any version of the lower- or full-body HBM marker sets. Because of this, the author had to create the required ZYX marker template from scratch. The author placed the appropriate markers onto a volunteer and collected a static T-pose of them. From this file, the author manually transcribed the required titles and coordinates of all 46 markers. Using this marker template within the Marker Matcher module not only enabled the self-paced mode and sphere control functionalities to work in tandem with HBM, but also allowed .mox files to be recorded. It also eliminated marker swapping during trials and reduced marker tracking difficulties in real-time. The author's 46-count marker template for the 2020 full-body HBM marker set is provided in Appendix G.

Chapter 5: Experimental Protocol

This study's experimental protocol and all study personnel were approved by USF's IRB with Pro#00040564. The lead author, PI, communicated with and scheduled participants, evaluated study applications, conducted walking trials, and gathered and handled all data. At least one assistant was present with the PI for every walking trial. They helped with calibrating equipment, preparing participants, note taking, and safety monitoring. Participants were required to attend a single session at USF. There were no alternatives for participating in this study. Participation was completely voluntary, and no monetary incentives or compensation were given to participants or study personnel. Participants were classified as controls, AFO-users, or FES-users. Controls did not use foot-drop devices during their sessions. Only pwMS comprised the AFO-user and FES-user groups. pwMS were required to bring and use their personal foot-drop device. There were no modifications to devices or changes in the way they were worn or operated. pwMS performed two multimodal walking trials: one with and one without their foot-drop device. Controls performed a single, unaided multimodal walking trial. Sessions for pwMS lasted around two hours, while sessions for controls lasted around one-and-a-half hours. Sessions for pwMS were longer because theirs included more rest periods, donning or doffing their foot-drop device, and two multimodal walking trials.

Study procedures were minimal, non-invasive, and labeled as extremely low risk due to the equipment used and the following: (1) participants were required to use their clinically prescribed and fitted devices for at least 30 days prior to participation; (2)

participants donned, doffed, and operated their devices as per their clinician's directions; (3) there were no alterations to foot-drop devices or ways in which they were worn or operated; and (4) there were no experimental procedures or interventions. Study risks were related to fatigue, trips and falls, and possible skin irritation from tape. However, these risks could be experienced in daily life, and each was clearly communicated and addressed with appropriate safety precautions: ample rest periods, use of a safety harness, and use of gentle medical tape, respectively.

Table 5.1 summarizes the walking trial types completed by each group; every participant completed an acclimation trial first. Acclimation trials differed from multimodal trials only in that their pitch remained at 0˚ (perfectly flat) the entire time. This allowed for easier familiarization with the self-paced mode and sphere control functionalities. Ensuring participants were comfortable with CAREN was crucial for getting them to walk as naturally as possible during their multimodal trial(s). Multimodal trials that used a device were labeled as aided; trials without devices were labeled as unaided. Fatigue is a very common and powerful MS symptom, and it can have a huge impact on performance and perception. Differences in learning capabilities can also skew results. Therefore, both must be addressed in the protocol.[23] This study addressed them by providing ample rest periods between trials and alternating the order of aided and unaided trials between participants within the AFO-user and FES-user groups.

Table 5.2 summarizes the procedures followed for each session. pwMS completed steps one through nine, while controls only needed to complete steps one through six. Before participants arrived, all equipment, worksurfaces, and touch-points were sanitized; CAREN and Nexus were booted up and calibrated; digital file pathways were set for data recording; and paper documents were prepared. During sessions, the raw XYZ

marker coordinates and force plate readings were recorded simultaneously within Nexus and D-Flow. Although these files contained duplicate information, the differing file types expanded post-processing options for data analysis. D-Flow's HBM-related .txt and .mox files were recorded in parallel to the above. Qualitative information was collected on participant data sheets (Appendix D), ratings of perceived exertion (RPE) questionnaires (Appendix H), and walking confidence questionnaires (Appendix I). In addition, black-and-white video of some walking trials were recorded.

Table 5.1: Required Walking Trials per Group

Group	Acclimation Trial	Unaided Trial	Aided Trial
Controls	✓	✓	✗
AFO-users	✓	✓	✓
FES-users	✓	✓	✓

Table 5.2: Experimental Protocol Summary

Step	Experimental Procedure Description
1	Process briefing, informed consent, and clothing and footwear check
2	Motion capture marker positioning and subject calibrations
3	Acclimation trial
4	Rest period
5	Aided/Unaided walking trial
6	Borg 6-20 RPE and 7-point Likert walking confidence questionnaires and rest period
7	Doffing/Donning device, marker repositioning, and subject recalibrations*
8	Unaided/Aided walking trial
9	Borg 6-20 RPE and 7-point Likert walking confidence questionnaires and marker removal

*Marker repositioning and recalibration was only performed if device placement required it.

Step 1 focused on handling documentation and ensuring participants completely understood the study and session proceedings. Once participants arrived at USF, the PI met them by their cars to give them a parking pass, then escorted them into the building.

Next, assistant(s) were introduced, and the IRB approved informed consent paperwork was reviewed. After the PI was certain participants understood everything and had all their questions answered, she collected their signatures on the paperwork and proceeded to fill out the participant data sheet, which includes finding the Patient-determined Disease Steps (PDDS)[38] with Appendix E. The knee and ankle widths recorded on this data sheet were measured with specialty calipers. The recorded weights and heights on the data sheet were participant reported, but accurate values were pulled from raw data for analysis. The PI provided participants with a pre-session checklist covering what, and what not, to wear upon scheduling their session. This checklist was systematically reviewed before moving on to Step 2. The PI carefully checked their attire for appropriateness and, if used, the condition of their foot-drop device. If shoes or clothing had reflective markings that interfered with the motion capture cameras, they were covered with gentle medical paper tape. If clothing was so loose that it interfered with marker positioning or obstructed markers during movement, they were adjusted. The PI asked participants to do one or more of the following to adjust loose clothing: tuck long shirts into pants, roll up long sleeves, tie up loose parts of shirts or pants with a hair tie or rubber band, or secure material with gentle paper tape. For long head or facial hair, the PI provided hair ties to braid and secure the hair out of the way of the safety harness and markers. All participants were required to wear their usual athletic, closed-toe shoes.

Step 2 focused on preparing participants for the walking trials. The PI discussed the calibration process, verbal directions that would be given during the proceedings, and poses required for calibrating the system to participants. The PI and an assistant then placed all 46 spherical, retroreflective markers (B&L Engineering; 14.00mm) on participants following Motek's 2020 full-body motion capture marker set. The PI created

a customized headband for participants to wear which contained the four head markers. The remaining 42 markers were secured to participants with specialty double-sided tape and medical paper tape. When foot-drop devices were involved, the PI inspected where they covered the participants' legs to determine if donning or doffing the device would require marker repositioning and subsequent recalibration within the system. Before participants were escorted onto the CAREN platform, they were fit with a full-body harness which was later secured to the harness support frame. This harness was required for safety purposes; it could fully support a participant's weight and prevent their knees from touching the ground in the event of a fall – which never occurred during these trials.

After participants were escorted onto the platform and secured to CAREN, the PI calibrated them first in Nexus and then in D-Flow. Nexus calibrations consisted of processing static T-pose and dynamic motion trials. T-pose was performed by standing upright with the head facing forwards, feet hip-width apart with the toes facing forwards, and arms raised shoulder height with the palms facing the floor. Participants were asked to pose in this way to the best of their abilities and to hold it for a few seconds. If they were unable to do the full T-pose, it was adapted and noted. Dynamic motion calibrations started with participants in the T-pose and progressed into them taking several steps at a comfortable pace without holding onto CAREN's handrails. The static and dynamic calibrations could take several minutes to process, so participants were offered a chair to sit on. Once Nexus calibrations were complete, participants were calibrated in D-Flow, which only took a minute and required a T-pose. First, they were calibrated within the HBM software and then within the Marker Matcher module for the self-paced mode and sphere control functionalities. Participants were instructed and encouraged to move and wave their hands around to get a feel for the sphere controls before proceeding.

Steps 3 and 4 were comprised of performing the acclimation trial and taking a rest before continuing. All trials began with a T-pose to make marker tracking and data analysis easier. Before and during every acclimation and multimodal walking trial, the PI instructed participants to walk at a comfortable pace, to move as they naturally would, and not to hold onto the handrails unless necessary. Participants were reminded that the primary task was to walk at a comfortable and normal pace, and the secondary task was hitting targets. Participants were discouraged from concentrating on hitting the targets if their posture or speeds became altered for extended periods of time. Examples are if they constantly held or moved their arms in preparation for hitting targets, if they notably changed their speed to hit targets, or if they changed their speeds out of frustration of missing targets. The rest period was optional but did not last more than 10 minutes if taken. For rest periods, participants were asked if they wanted to come off of CAREN to sit and have water, or if they wanted to stay on CAREN and have a chair brought to them.

Steps 5 and 6 were treated as a unit. Immediately after completion of a multimodal walking trial, participants were removed from CAREN so they could sit and complete two qualitative questionnaires: the Borg 6-20 RPE[39] and a custom-made 7-point Likert scale for walking confidence. If the participant was a control, this was the end of their session. If they were part of the AFO-user or FES-user groups, they were instructed to don/doff their device as part of Step 7. Steps 8 and 9 were treated as a unit and were conducted identically to Steps 5 and 6. Once the final multimodal trial and questionnaires were completed, participants were helped out of the harness and had all 46 markers removed. When they were ready to leave, they were thanked for their time and escorted out of the building. Once participants left, the equipment was sanitized, data was processed in GOAT, and all files were uploaded into the IRB approved Box account.

Chapter 6: Data Analysis

This study's goal is to explore how multimodal walking impacts quantitative and qualitative aspects of gait for pwMS who use AFO and FES foot-drop interventions. Although a plethora of information was collected, this dissertation only needed a focused subset to achieve its goal. The variety of recorded information was intended to support a range of future studies centered on multimodal walking environments. The primary outcome measures (OMs) of this study pertain to quantitative aspects of gait: overall mobility, gait symmetry (including degree of asymmetry), and orthotic gait. The mobility parameters are walking speed, step width, step length, step time, stride time, stance time, swing time, cadence, and percentage of time spent in the single and double support phases of ambulation. The gait symmetry parameters are stance time, swing time, step length, step time, and percentage of time spent in the stance, swing, and single support phases of ambulation. Orthotic gait is evaluated for each mobility and symmetry parameter listed above for all pwMS. The secondary OMs pertain to qualitative aspects of gait: RPE and confidence in walking ability. Both of these OMs utilized questionnaires. Walking trial results within each study group were examined for trends and possible correlations between participant demographics and all of the OMs listed above. The averages of each group's OM parameters were also compared to one another. This dissertation provides analysis of a normative cohort of thirteen participants aged 28 to 64 years; a cohort of three AFO-users aged 58 to 63 years; and a case study of a pwMS, 58 years of age, who used two types of AFOs and an FES device.

6.1 Analysis Methodology

For the primary OMs, version 4.2 of Motek's GOAT software was used to process the .mox files created within HBM. GOAT creates gait reports, .csv files of the processed parameters, force vector overlays on black-and-white video recordings, and three-dimensional animations of retroreflective markers. The .csv files, vector overlays, and animations are useful for generating plots, developing trial performance observations, and creating visuals for presentations. GOAT detects the first and last steps of each walking trial and performs calculations in between those indices. Gait reports provide the averages and standard deviations of a variety of spatiotemporal gait parameters for both overall gait and the left and right legs independently, which is extremely useful for calculating degree of asymmetry during ambulation. The data within these gait reports were used to create the mobility and symmetry parameter result tables found in Appendix J. These results were used to calculate the percent deviations within each participant's trial, which provide normalized values that are easier to interpret; differences and percent differences between the left and right symmetry parameters, which facilitates evaluation of degree of asymmetry; and orthotic effects for pwMS.

Four GOAT settings were used to generate the gait reports: (1) 'Step Detection' was reprocessed using a marker-based method; (2) kinematics and kinetics were reprocessed within the 'Kinematics/Kinetics/Muscles' settings, but the muscle forces were not available for processing; (3) 'Gait' was reprocessed using the same marker-based method specified for step detection; and (4) 'Cycles' was instructed to add all valid gait cycles after loading the .mox file. Once GOAT processed a selected .mox file, the 'MM Gait Report' and its associated .csv file were exported and referenced for the creation of the summary tables found in Appendix J.

The secondary OMs were evaluated using the results of the RPE and walking confidence questionnaires. Because both of these qualitative outcomes utilized Likert scales, both could be evaluated objectively and quantitatively; allowing group averages to be calculated and compared to one another. The Borg 6-20[39] was used for determining RPE, whereas the author designed a 7-point Likert scale to evaluate walking confidence because a standardized psychometric test does not exist. This dissertation also provides a variety of anecdotal information from the PI's observations, participant feedback regarding the experimental setup and environment, and insights from pwMS regarding their experiences with foot-drop and foot-drop interventions.

6.2 The Control Group

Inclusion of a control group validated the experimental protocol and provided normative values to compare against pwMS – which was important given the novelty of the testing environment. Walking performance for controls was evaluated within the group by comparing individual trials to one another, and as a group through calculation of group averages and standard deviations for each parameter. The analyzed parameters encompass all those stated at the beginning of this chapter, excluding orthotic gait as controls did not use foot-drop interventions. For qualitative OMs, simple algebra was used to produce group averages and standard deviations. Calculation of group averages and standard deviations for quantitative OMs used participants' trial averages as produced by GOAT. To better interpret the performance variability between participants' mobility and symmetry parameters, the percent deviations of their standard deviations were calculated with the following equation, where σ is each participant's standard deviation and μ is their mean over the course of the entire multimodal trial:

$$Percent\ Deviation\ for\ Performance\ Variability = \frac{\sigma}{\mu} * 100\%$$

These percent deviations provide normalized values that make understanding the magnitude of walking performance variability easier to interpret and make comparing variabilities across participants more appropriate. Degree of asymmetry was similarly evaluated using a percent difference and also relied on processed data from GOAT:

$$Degree\ of\ Asymmetry = \frac{Left\ Mean\ Value\ -\ Right\ Mean\ Value}{[(Left\ Mean\ Value + Right\ Mean\ Value)/2]} * 100\%$$

6.3 The AFO-user Group

Analysis of the AFO-users' aided and unaided multimodal walking trials followed all of the same processes as outlined above for the control group. The overall AFO-user group's results were compared to the control group's results. In addition, orthotic gait was analyzed to understand the impacts of AFO usage. Orthotic effects were calculated for every mobility and gait symmetry parameter. Unaided trials were used as baselines for all evaluations. The differences and percent orthotic effects between participant's aided and unaided trials were found. Percent orthotic effects provide normalized values that are more straightforward to interpret and appropriate to compare. The equations used for calculating orthotic gait effects are as follows:

$$Orthotic\ Effect = Aided\ Value - Unaided\ Value$$

$$Percent\ Orthotic\ Effect = \frac{Aided\ Mean\ Value - Unaided\ Mean\ Value}{Unaided\ Mean\ Value} * 100\%$$

6.4 The Case Study

This dissertation's original recruitment goals could not be obtained due to forces outside of the PI's control and are discussed in Chapter 7. In place of a full FES-user group, a case study was performed on an individual who used multiple foot-drop interventions, including an FES device. The case study completed walking trials with

three different foot-drop devices over three separate sessions to avoid fatigue and learning from skewing results. Analysis of the case study's trials followed all of the same processes as outlined above for the AFO-user group. The results from each device were compared against one another, the AFO-user group, and the control group. As will be discussed in Chapter 8, the case study participant did not experience any significant changes in her health, activities, or device usage between her sessions, and she performed her aided walking trial before her aided trial during her first session. Therefore, her initial, unaided walking trial was used as the baseline for calculating the orthotic effects of each device she used.

Chapter 7: Results

Recruitment and testing began in September 2021 and ended in December 2022. The original recruitment goal totaled thirty participants divided as follows: ten controls, ten AFO-users, and ten FES-users. Challenges imposed by the covid-19 pandemic forced the PI to use convenience samples instead of the original goals. The pandemic has had a wide variety of societal effects long after the US government lifted most restrictions. Because pwMS are immunocompromised, many dramatically changed their lifestyles in response to covid-19 to stay safe. After interviewing Morsani's MS division director and several pwMS, the PI discovered that pwMS were not only reducing their social interactions and outings, but also their doctor visits. Some simply postponed their appointments while others switched to telehealth visits unless something was medically necessary. In addition, Morsani's MS clinic limited premises access to employees and patients during the height of the pandemic, and it only relaxed those regulations in mid-to-late 2022. This inhibited recruitment as the original strategy relied heavily on the PI performing outreach at the Morsani clinic. Furthermore, local MS support groups experienced dramatic downturns in active members. During the pandemic, support groups either ceased activities or switched to periodic virtual meetings, and several of the smaller groups never reopened. Two of the most prominent MS support groups in the Hillsborough area only resumed in-person and hybrid meetings in 2022. Although recruitment efforts utilized neurologist referrals, outreach with MS support groups, fliers, emails, and phone calls, reaching and retaining the required audience proved quite

difficult. The original recruitment goals had to be converted to convenience samples to adapt to these circumstances. This resulted in the FES-user group being replaced with a case study of a single pwMS who used an FES device and two different types of AFOs. Even with recruitment challenges, three styles of foot-drop interventions were tested, providing unique insights into their effects on gait within a multimodal environment.

7.1 Recruitment Totals and Demographics

This dissertation presents a total of sixteen participants: thirteen controls aged 28 to 64 years and three pwMS aged 58 to 63 years – one of which also comprises the case study. Unexpectedly, all three pwMS used the same model of AFO: Ottobock's carbon fiber Walk-On Flex. The case study participant performed aided trials with the Ottobock, WalkAide's FES device, and a plastic, hinged AFO that was custom formed by an orthotist. To avoid fatigue and learning from affecting results, the case study's walking trials were completed over three different sessions, where each session was separated by several weeks. Ultimately, this dissertation analyzed five different aided walking trials: three with Ottobock's AFO, one with a hinged AFO, and one with WalkAide's FES device. Participant demographics and foot-drop device information are summarized below. The order in which pwMS conducted their aided versus unaided trials was alternated to address learning and fatigue, factors that could affect results. The case study participant and AFO-usre_03 conducted their aided trials before their unaided trials, while AFO-user_02 conducted her unaided trial before her aided trial.

Table 7.1: Basic Participant Demographics

Participant	Age (years)	Gender (from birth)	Height (m)	Weight (kg)
control_01	58	Female	1.60	59.5
control_02	65	Male	1.75	101.6
control_03	57	Male	1.70	84.4
control_04	48	Female	1.68	78.1
control_05	46	Male	1.79	80.2
control_06	60	Female	1.60	64.0
control_07	64	Female	1.57	60.7
control_08	35	Male	1.70	71.4
control_09	40	Female	1.68	80.8
control_10	32	Female	1.75	85.2
control_11	34	Male	1.80	92.5
control_12	28	Female	1.60	74.8
control_13	29	Male	1.93	93.8
AFO-user_01*	58	Female	1.60	67.3
AFO-user_02	61	Female	1.65	103.6
AFO-user_03	63	Female	1.68	77.4
AFO-user_04*	58	Female	1.60	62.4
FES-user_01*	58	Female	1.60	65.3

*Case study participant who completed three sessions separated by several weeks and used an Ottobock AFO, hinged AFO, and WalkAide.

Table 7.2: MS Diagnosis Information

Participant	Type of MS	Year of Diagnosis	Foot-drop Affecting	Dalfampridine User	PDDS**
AFO-user_01* **AFO-user_04*** **FES-user_01***	RRMS	1992	Right	No	4
AFO-user_02	PPMS	2010	Left	Yes	4
AFO-user_03	PPMS	2012	Right	Yes	5

*Case study participant who completed three sessions separated by several weeks and used an Ottobock AFO, hinged AFO, and WalkAide.
**PDDS stands for Patient-determined Disease Steps – see Appendix E.

Table 7.3: Foot-drop Device Information

Participant	Maker & Model/Material	Years of Ownership	Hours Used per Day
AFO-user_01*	Ottobock Walk-On Flex / Carbon fiber	10	2
AFO-user_02	Ottobock Walk-On Flex / Carbon fiber	8	8
AFO-user_03	Ottobock Walk-On Flex / Carbon fiber	6	1-8
AFO-user_04*	Orthotist Custom Formed Hinged / Plastic	0.5	4
FES-user_01*	WalkAide	3	2

*Case study participant who completed three sessions separated by several weeks and used an Ottobock AFO, hinged AFO, and WalkAide.

According to the MS division director at Morsani, the majority of MS patients in 2021 who required foot-drop devices were between 45 and 65 years of age, and the gender ratio was approximately 3:2 women to men. The PI prioritized recruiting controls who fell within those parameters to create an appropriate control group. The final control group ranged from 28 to 64 years of age with seven female and 6 male participants. All three participants with MS were female, matched the age range of Morsani's patients, and were close in age, height, and PDDS. One pwMS had been diagnosed with RRMS for 30 years, while the others were diagnosed with PPMS for 10 and 12 years. Ownership of the Ottobock Walk-On Flex ranged from 6 to 10 years. The case study participant owned her WalkAide for 3 years and a hinged AFO for 6 months. It was difficult for all three pwMS to estimate their daily device usage because it could fluctuate between 1 to 2 hours of intermittent to over 8 hours of consistent usage. Device usage depended on if they were venturing outside of their homes or doing something physically demanding. Therefore, the values provided in Table 7.3 are rough estimations. Lastly, the control group's weight ranged from 59.5 to 101.6 kg (79.0 kg average), the case study participant's weight ranged from 62.4 to 67.3 kg (65.0 kg average), and the AFO-user group's weight ranged from 62.4 to 103.6 kg (82.0 kg average).

All three pwMS experienced imbalance and exhibited compensatory motions that affected their gait. They all voiced fatigue and heat sensitivity as prominent symptoms that limited their physical and social activities. Two pwMS used dalfampridine to assist with ambulation, but the other could not use it due to her DMT prescription. AFO_user_02 experienced paralysis in her left arm and relied on assistive devices (canes and walkers) to stay balanced while ambulating. AFO_user_03 suffered more extreme imbalance than the other participants and relied on assistive devices and a service dog to safely ambulate. Both AFO_user_02 and AFO_user_03 held onto CAREN's handrails throughout most of their walking trials, but they still attempted to hit targets on occasion.

To gauge the physical condition and habits of participants, information about their regular physical activities (type, duration, and intensity) were gathered on the participant data sheet and are summarized in Table 7.4. Activities were classified as weekday and weekend to differentiate daily/weekly routines from more unique, recurring activities that may be weekend-dependent. The intensity of each activity was rated as easy, medium, or hard via the descriptive Likert scale seen in Appendix D. Most participants walked daily and rated this activity as easy. Participants who conducted more aerobic-type activities tended to rate them as medium; these activities included biking, swimming, hiking, and running. On average, the control group rated weekday activities as easy while pwMS rated theirs as medium. Although all sixteen participants completed weekday activities, only seven performed weekend activities. This does not necessarily mean that participants were inactive; but if they were active, their weekend activities were the same as their typical weekday activities. Lastly, the duration of physical activities varied widely (0.5 to 6 hours) between both controls and pwMS. Weekday activities averaged 1.23 hours to 1.42 hours for controls and 2.94 hours to 3.28 hours for pwMS.

Table 7.4: Estimated Physical Activities

Participant	Weekday Physical Activities			Weekend Physical Activities		
	Hours	**Intensity**	**Types**	**Hours**	**Intensity**	**Types**
control_01	0.5	Easy	Walking	NA	NA	NA
control_02	1	Easy	Walking	2	Easy	Golfing
control_03	0.5 0.5	Easy Medium	Walking Swimming, weight training	0.5	Easy	Walking
control_04	1	Medium	Yoga, biking, walking	NA	NA	NA
control_05	1	Medium	Biking, walking	NA	NA	NA
control_06	1.5	Medium	Weight training, gardening	3	Medium	Yard work
control_07	1	Easy	Weight training, core, stretching	NA	NA	NA
control_08	1.5	Easy	Walking	2-3	Medium	Waking, hiking, running, weight training
control_09	0.5-1	Easy	Walking, house chores	NA	NA	NA
control_10	1-2	Easy	Walking Gardening	4	Easy	Hiking, walking, gardening
control_11	2	Easy	Walking	4	Easy	Hiking, walking
control_12	3-4	Medium	Hiking, walking	NA	NA	NA
control_13	1	Easy	Walking	NA	NA	NA
AFO-user_01* **AFO-user_04*** **FES-user_01***	6 0.5	Easy Medium	Walking Weight training	2	Medium	Swimming, biking
AFO-user_02	0.3	Medium	Housework	NA	NA	NA
AFO-user_03	2-3	Medium	Walking, housework	NA	NA	NA

*Case study participant who completed three sessions separated by several weeks and used an Ottobock AFO, hinged AFO, and WalkAide.

7.2 Experimental Results

Motek's GOAT software was used to process all multimodal walking trials. The results (averages and standard deviations) for each spatiotemporal parameter of interest are summarized in Appendix J. These results are grouped into overall mobility and gait symmetry tables for controls and pwMS (including aided and unaided trials). This chapter provides synopses of Appendix J's tables; calculations of percent deviations within trials, degree of asymmetry, and orthotic gait; and results from the qualitative questionnaires.

7.2.1 The Control Group

Tables J.1 and J.3 provide the control group's overall mobility and gait symmetry parameters, respectively. Group averages and standard deviations for each parameter were calculated using individual trial averages. The degree of asymmetry was calculated with data from Table J.3. Walking performance variability, as determined with the percent differences of participants' standard deviations, was calculated for both Table J.1 and J.3. Parameters within summary tables were compared against one another, participant demographics, physical activities, RPE, and walking confidence scores. Lastly, the qualitative results for RPE and walking confidence were examined for trends.

7.2.1.1 Overall Mobility Parameters

There were no correlations between participants' mobility parameters and their demographics (age, gender, height, and weight), physical activities, RPE, or walking confidence scores. Two mobility parameter pairings were suitable for head-to-head comparisons: (1) time spent in the swing versus stance phases of the gait cycle and (2) the percentage of time spent in single (total per leg) versus total double support. Across all controls, the amount of time spent in the stance phase was approximately twice that spent in the swing phase. The differences between percentage of time spent in single (total per

leg) and total double support ranged from 0.22 to 6.82 and averaged 1.70; where seven persons had higher percentages of time spent in double support than single.

The variability within participants' walking trails was investigated using Table 7.5. These normalized percent deviations per participant allowed performance variabilities to be compared across participants and group averages to be calculated. Walking speed and step width had the largest variabilities across all controls. Controls averaged 20% variability in step width and 17% in walking speed. The group's average variabilities for step length and stride length were 11% and 10%, respectively. The remaining mobility parameters averaged between 5% and 9% variability. Eleven of the thirteen controls exhibited higher variability in their step widths than their step lengths. Six of those eleven had two to three times higher variability in width than length, while the other five differed by 3% to 11%. Two controls opposed this trend as the variability in their step lengths were greater than their step widths, but the differences were only 1% and 4%. Eight of the thirteen controls had slightly higher variability in their swing times than stance times, two controls had equal variabilities between these parameters, and three had slightly higher variability in stance time than swing time. Eleven of the thirteen controls had slightly higher variability in percentage of time spent in the double support phase than single. Lastly, there were no discernable trends between parameters' normalized variabilities and participant demographics, physical activities, RPE, or walking confidence scores.

Table 7.5: Variability within Control's Mobility Parameters

Participant	Walking Speed	Cadence	Step Width	Step Length	Stride Length	Step Time	Stride Time	Stance Time	Swing Time	Single Support (total per leg)	Total Double Support
control_01	22%	7%	33%	13%	13%	7%	7%	9%	5%	7%	8%
control_02	13%	6%	27%	10%	9%	6%	4%	4%	5%	7%	9%
control_03	26%	8%	14%	18%	17%	8%	6%	9%	10%	7%	11%
control_04	18%	5%	17%	14%	13%	6%	5%	6%	6%	4%	7%
control_05	17%	6%	17%	11%	10%	8%	4%	6%	5%	7%	9%
control_06	16%	5%	19%	9%	9%	5%	3%	8%	10%	8%	9%
control_07	18%	13%	25%	14%	12%	9%	6%	7%	8%	5%	11%
control_08	18%	7%	22%	13%	13%	5%	4%	5%	5%	7%	8%
control_09	14%	5%	25%	6%	6%	6%	5%	7%	3%	4%	7%
control_10	16%	5%	13%	9%	8%	5%	4%	6%	5%	3%	5%
control_11	18%	17%	13%	14%	14%	10%	4%	7%	11%	13%	14%
control_12	15%	4%	17%	8%	7%	4%	4%	4%	5%	6%	7%
control_13	15%	6%	16%	5%	5%	6%	4%	6%	7%	9%	11%
control_group (mean)	17%	7%	20%	11%	10%	6%	5%	6%	7%	7%	9%

7.2.1.2 Gait Symmetry Parameters

Table J.3 provides the left and right leg parameters provided by GOAT. Degree of asymmetry was evaluated as the percent difference between these left and right leg values. The results are provided in Table 7.6, where negative signs indicate that right values were greater than left values. The control group averaged 1% difference for stance time and percentage of time spent in stance; 2% difference for step time, swing time, and both

percentages of time spent in swing and single support; and 4% difference for step length. Again, there were no correlations to participant demographics, physical activities, RPE, or walking confidence scores. Lastly, Table 7.7 presents the variability in participant performances for the gait symmetry parameters. The majority of participants had negligible differences between their left and right leg variabilities, but the group as a whole exhibited differences ranging from 0% to 10%.

Table 7.6: Degree of Asymmetry for Controls

Participant	Step Length	Step Time	Stance Time	Swing Time	Stance	Swing	Single Support
control_01	-2%	0%	0%	3%	-1%	2%	-4%
control_02	4%	0%	-1%	3%	-1%	1%	-3%
control_03	4%	-3%	2%	-5%	2%	-4%	2%
control_04	7%	-2%	2%	-3%	1%	-2%	3%
control_05	-5%	3%	-2%	5%	-2%	4%	-3%
control_06	0%	-2%	-1%	0%	0%	1%	-1%
control_07	-7%	-2%	-1%	0%	-1%	2%	2%
control_08	-8%	-4%	0%	0%	1%	-1%	2%
control_09	-2%	2%	0%	0%	0%	0%	0%
control_10	2%	-3%	1%	-3%	1%	-2%	2%
control_11	-4%	0%	0%	0%	0%	0%	1%
control_12	2%	-2%	0%	-3%	0%	-1%	0%
control_13	-4%	-2%	0%	0%	0%	-1%	0%
control_group (|mean|)	4% ± 2%	2% ± 1%	1% ± 1%	2% ± 2%	1% ± 1%	2% ± 1%	2% ± 1%

*Group mean is the average of |individual values|

Table 7.7: Variability within Control's Symmetry Parameters

Participant / Parameter	Step Length		Step Time		Stance Time		Swing Time		Stance		Swing		Single Support	
	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg
control_01	17%	9%	8%	7%	9%	8%	8%	5%	3%	2%	6%	5%	8%	5%
control_02	10%	10%	4%	6%	4%	4%	5%	3%	2%	2%	4%	3%	4%	9%
control_03	17%	18%	8%	8%	10%	9%	13%	7%	5%	3%	12%	7%	7%	7%
control_04	10%	15%	4%	6%	6%	6%	3%	6%	2%	3%	4%	5%	3%	5%
control_05	9%	12%	5%	10%	5%	6%	5%	5%	2%	3%	3%	6%	5%	8%
control_06	12%	6%	7%	3%	9%	5%	13%	3%	8%	2%	16%	3%	12%	3%
control_07	14%	11%	10%	9%	9%	7%	8%	8%	3%	3%	7%	6%	4%	6%
control_08	12%	13%	7%	5%	5%	5%	3%	5%	2%	3%	4%	5%	8%	4%
control_09	8%	6%	6%	6%	7%	6%	3%	5%	2%	2%	4%	4%	4%	4%
control_10	9%	9%	5%	5%	6%	6%	5%	5%	2%	2%	4%	3%	3%	3%
control_11	16%	12%	10%	8%	6%	7%	9%	11%	5%	5%	9%	11%	16%	9%
control_12	10%	5%	5%	3%	4%	4%	5%	3%	3%	1%	5%	3%	9%	3%
control_13	6%	5%	6%	6%	6%	6%	7%	7%	3%	3%	7%	7%	9%	8%
control_group (mean)	11%	10%	6%	6%	7%	6%	7%	6%	3%	3%	7%	5%	7%	6%

7.2.1.3 Qualitative Parameters

Results from the Borg 6-20 RPE and walking confidence questionnaires are provided in Table 7.8. The Borg 6-20's scale ranges from 6 to 20, where 6 corresponds to 'no exertion' and 20 to 'maximal exertion.' Therefore, larger RPE values represent higher amounts of perceived exertion during multimodal walking trials. RPE values for controls ranged from 7 ('extremely light) to 11 ('light') and averaged 9 ('very light'). The PI's custom Likert scale for walking confidence ranges from 1 to 7, where 1 corresponds to 'very confident' and 7 to 'very unconfident.' The control group's confidence in their ability to walk during multimodal trials ranged from 1 ('very confident') to 3 ('somewhat confident') and averaged 2 ('confident'). No reliable connections were seen between these qualitative results and participant demographics or physical activities.

Table 7.8: Qualitative Questionnaire Results for Controls

Participant	Borg 6-20 RPE	Walking Confidence
control_01	8	3
control_02	10	1
control_03	11	2
control_04	8	1
control_05	9	2
control_06	9	3
control_07	11	1
control_08	7	2
control_09	9	2
control_10	9	3
control_11	7	1
control_12	7	2
control_13	9	3
control_group	9 ± 1	2 ± 1

7.2.2 Participants with Multiple Sclerosis

Tables J.2 and J.4 contain the overall mobility and gait symmetry parameter tables for all pwMS and provide unaided and aided group averages for the AFO-user group. Tables include the case study's FES trial for brevity and to make comparisons easier. The case study itself has a dedicated section in Chapter 8 where it is discussed in detail with focused data tables for results interpretation. Every analysis performed on controls was performed on participants with MS. However, the small and all female sample size prevented correlations from being discerned between walking performance results and participant demographics (including MS type, time since MS onset, and PDDS) or physical activities. The orthotic effects of devices were calculated as the differences between aided and unaided walking trials, where unaided trials were used as baselines.

7.2.2.1 Overall Mobility Parameters

Similar to control participants, all pwMS spent approximately twice the amount of time in the stance phase of the gait cycle than in the swing phase; and this held true for both aided and unaided trials – see Table J.2. The differences between percentage of time spent in single (total per leg) and total double support ranged from 1.57 to 23.46 for unaided trials and 1.28 to 18.35 for trials that used AFOs. The FES trial had the lowest difference between these parameters at 0.29. For both their aided and unaided trials, AFO-user_01 and AFO-user_02 spent a higher percentage of time in total double support than single support. FES-user_01 similarly spent more time in total double than single support, but only by a small margin. AFO-user_04 spent a higher percentage of time in single support. Lastly, AFO-user_03 spent a higher percentage of time in single support than double support for both her aided and unaided trials.

Table 7.9 presents performance variability as normalized percent deviations per participant for each mobility parameter. Unlike controls, pwMS did not exhibit a consistent overarching pattern. Parameter variability differed widely between participants, and the descending order of parameters based on variability tended to change between a participant's aided and unaided trials. The case study participant maintained the most consistency in her performance variabilities. As AFO-user_01, her unaided and aided trials had the highest variability in step width and second highest in walking speed – which mirrored the control group's pattern. As AFO-user_04, her step width also had the highest variability, but three parameters were tied for second place: walking speed, step length, and step time. Lastly, as FES-user_01, she again experienced the highest variability in her step width, but this time it was followed by both walking speed and step time for second highest variability. During AFO-user_02's unaided trial, walking speed had the highest variability followed by step length. But during her aided trial, swing time had the highest variability followed by walking speed. Finally, AFO-user_03's unaided trial had an unusually high variability, 125%, in her stride length followed by step width at 38%. During her aided trial, step width had the highest variability followed by walking speed – which mirrored the control group's pattern. For unaided multimodal walking trials, pwMS as a group had the highest variability in stride length at 52%. AFO-user_03's high stride length variability may be an outlier or could indicate that she alternated between very short, unsure steps and longer, confident strides. The group's unaided averages also revealed the mobility parameters with the second and third highest variabilities as walking speed at 24% and step width at 23%. For aided multimodal trials, the AFO group experienced the highest variability in their step width at 19% followed by walking speed at 18%.

Table 7.9: Variability within pwMS's Mobility Parameters

Participant	Walking Speed	Cadence	Step Width	Step Length	Stride Length	Step Time	Stride Time	Stance Time	Swing Time	Single Support (total per leg)	Total Double Support
AFO-user_01* (Unaided)	17%	11%	23%	14%	11%	11%	6%	8%	6%	5%	7%
AFO-user_01* (Ottobock)	13%	9%	17%	11%	9%	9%	5%	6%	6%	5%	6%
AFO-user_02 (Unaided)	29%	14%	9%	23%	21%	15%	6%	9%	16%	8%	7%
AFO-user_02 (Ottobock)	26%	13%	11%	19%	18%	18%	6%	12%	38%	19%	16%
AFO-user_03 (Unaided)	25%	18%	38%	19%	125%	16%	6%	13%	22%	21%	26%
AFO-user_03 (Ottobock)	19%	12%	25%	11%	9%	13%	7%	10%	11%	12%	18%
AFO-user_04* (Hinged)	13%	12%	25%	13%	9%	13%	5%	6%	10%	7%	7%
FES-user_01* (WalkAide)	13%	12%	33%	11%	8%	13%	6%	8%	6%	5%	5%
AFO_group (Unaided mean)	24%	14%	23%	18%	52%	14%	6%	10%	15%	11%	14%
AFO_group (Aided mean)	18%	12%	19%	13%	11%	13%	6%	9%	16%	11%	12%

*Case study participant who completed three sessions separated by several weeks.

7.2.2.2 Mobility Parameter Statistical Significance Testing

pwMS were divided into two groups: an AFO-user group and a case study. The AFO-user group consists of three participants who produced three unaided trials and four aided trials. The case study produced one unaided trial and three aided trials, each using a different foot-drop device. The eleven mobility parameters discussed in the preceding section were evaluated for statistical significance for both the AFO-user group and case

study. The AFO-user's unaided and aided trials were compared against controls using independent t-tests. Each of the case study's trials were compared against controls using t-tests as well. Matlab's ttest2 function was used for these analyses and used participant's parameters averages (as shown in Appendix J) for all calculations. Only p-values equal to or less than 0.05 were considered as showing statistically significant differences.

For the AFO-user's t-tests, the degrees of freedom for all unaided calculations were 14, and for all aided calculations it was 15. The results are summarized in the Table 7.10 below. Depending on the parameter, use of an AFO either lowered p-values or increased them – meaning that device usage had mixed results for reducing statistically significant differences between pwMS and controls. There are four instances where statistical significance was present: unaided step length, aided and unaided stride length, and aided stride time. These can be interpreted as AFOs improving step length significantly and worsening stride time significantly when compared to controls. For the AFO group's stride length, both their aided and unaided trials had the same p-value, but the t-statistic was lower with the use of AFOs.

The case study's t-test results are presented in Table 7.11, where the degrees of freedom were 12 for all calculations. Again, the changes in p-values across each trial type illustrate the varied impacts devices had on mobility parameters. Looking over each parameter, there are very few instances of p-values remaining the same, or nearly the same, across the case studies four trials. For cadence, the case study demonstrated statistically significant differences from the control group for her unaided, Ottobock, and hinged AFO trials; but her WalkAide trial was not statistically significantly different than the control group's cadence. This means that the case study participant's cadence was only statistically comparable to the control group's when she used the WalkAide. For both step

and stride length, only the unaided trials were statistically significantly different from those of controls. This means that the use of each foot-drop device improved her step and stride lengths significantly, but some generated slightly more improvements than others.

Table 7.10: T-test Results for AFO-users

Participant	AFO group (Unaided)	AFO group (Aided)
Walking Speed	tstat = 1.952 p = 0.07	tstat = 0.288 p = 0.78
Cadence	tstat = -1.303 p = 0.21	tstat = 1.155 p = 0.27
Step Width	tstat = 0.126 p = 0.90	tstat = 1.056 p = 0.31
Step Length	tstat = 2.878 p = 0.01	tstat = 1.848 p = 0.08
Stride Length	tstat = 5.341 p = 0.00	tstat = 3.636 p = 0.00
Step Time	tstat = 0.956 p = 0.36	tstat = 1.846 p = 0.08
Stride Time	tstat = 0.867 p = 0.40	tstat = 2.156 p = 0.05
Stance Time	tstat = 0.208 p = 0.84	tstat = 1.757 p = 0.10
Swing Time	tstat = 1.415 p = 0.18	tstat = 1.595 p = 0.13
Single Support (total per leg)	tstat = 1.922 p = 0.75	tstat = 0.961 p = 0.35
Total Double Support	tstat = -1.925 p = 0.07	tstat = -0.855 p = 0.41

*Degree of freedom was 14 for all unaided calculations and 15 for all aided calculations.

Table 7.11: T-test Results for Case Study

Trial	Unaided	Ottobock AFO	Hinged AFO	WalkAide FES
Walking Speed	tstat = 0.702 p = 0.50	tstat = 0.440 p = 0.67	tstat = -0.677 p = 0.51	tstat = -0.217 p = 0.83
Cadence	tstat = -2.481 p = 0.03	tstat = -2.281 p = 0.04	tstat = -2.281 p = 0.04	tstat = -1.682 p = 0.12
Step Width	tstat = 0.425 p = 0.68	tstat = 0.676 p = 0.51	tstat = 1.178 p = 0.26	tstat = 1.429 p = 0.18
Step Length	tstat = 2.225 p = 0.05	tstat = 1.947 p = 0.08	tstat = 0.835 p = 0.42	tstat = 0.974 p = 0.35
Stride Length	tstat = 2.222 p = 0.05	tstat = 1.949 p = 0.08	tstat = 0.785 p = 0.45	tstat = 0.922 p = 0.37
Step Time	tstat = 1.763 p = 0.10	tstat = 1.943 p = 0.08	tstat = 1.763 p = 0.10	tstat = 1.402 p = 0.19
Stride Time	tstat = 1.864 p = 0.09	tstat = 1.864 p = 0.09	tstat = 1.864 p = 0.09	tstat = 1.405 p = 0.18
Stance Time	tstat = 1.827 p = 0.09	tstat = 1.698 p = 0.12	tstat = 1.955 p = 0.07	tstat = 1.313 p = 0.21
Swing Time	tstat = 1.026 p = 0.33	tstat = 1.026 p = 0.33	tstat = 0.922 p = 0.37	tstat = 0.828 p = 0.43
Single Support (total per leg)	tstat = 0.376 p = 0.71	tstat = 0.252 p = 0.81	tstat = -0.900 p = 0.38	tstat = -0.070 p = 0.95
Total Double Support	tstat = -0.388 p = 0.70	tstat = -0.298 p = 0.77	tstat = 0.965 p = 0.35	tstat = 0.064 p = 0.95

*Degree of freedom was 12 for all calculations.

7.2.2.3 Gait Symmetry Parameters

For all pwMS, Table J.4 provides their aided and unaided left and right leg parameters for evaluation of gait symmetry. Degree of asymmetry was evaluated as the percent difference between these left and right leg values. The results are provided in Table 7.10, where negative signs indicate that right values were greater than left values. Group averages were calculated using the absolute value of individual results. Degree of

asymmetry ranged from 0% to 28% for unaided trials, 2% to 19% for AFO aided trials, and 3% to 20% for the FES aided trial. As a group, AFO-users had the highest asymmetry in step time for both unaided and aided trials at 19% and 13%, respectively. For unaided trials, the group's swing time had the second highest asymmetry at 15%, followed by percentage of time spent in the swing phase at 14%. Step length and percentage of time spent in single support were tied at 11% for unaided trials; lastly with 6% differences, stance time and percentage of time spent in stance were also tied. For aided trials, the AFO-user group had the second highest degree of asymmetry in step length at 10%. Three parameters were tied for third highest degree of asymmetry in aided trials: swing time and percentages of time spent in the swing phase and in single support. Once again, the group's average stance time and percentage of time spent in stance were tied as the most symmetrical gait parameters, but this time with a 4% difference between the left and right legs during aided trials with AFOs.

Table 7.11 shows participant variabilities for the gait symmetry parameters that are summarized in Table J.4. The left and right leg variabilities changed between participant's aided and unaided trials, and the descending order of variability differed between participants. Performance variability ranged from 2% to 25% for unaided trials, 2% to 55% for AFO trials, and 2% to 8% for the FES trial. On average for unaided trials, pwMS presented higher variability in their right legs for step length, swing time, and percentages of time spent in stance, swing, and single support. The differences between the right and left leg values for those parameters ranged from 1% to 5%. The MS group's average, unaided stance time variabilities for the left and right legs were equivalent at 9%. In contrast, The AFO-user group's average variability for the right leg was higher than the left for all symmetry parameters, where differences between legs ranged from 1% to 5%.

Table 7.12: Degree of Asymmetry for pwMS

Participant	Step Length	Step Time	Stance Time	Swing Time	Stance	Swing	Single Support
AFO-user_01* (Unaided)	5%	-17%	0%	-3%	1%	-3%	5%
AFO-user_01* (Ottobock)	4%	-15%	2%	-6%	2%	-5%	6%
AFO-user_02 (Unaided)	6%	23%	-5%	13%	-4%	13%	-6%
AFO-user_02 (Ottobock)	12%	12%	-4%	15%	-5%	13%	-13%
AFO-user_03 (Unaided)	23%	17%	-13%	28%	-13%	26%	-21%
AFO-user_03 (Ottobock)	11%	8%	-7%	6%	-5%	9%	-7%
AFO-user_04* (Hinged)	15%	-19%	2%	-9%	4%	-8%	11%
FES-user_01* (WalkAide)	9%	-20%	3%	-6%	3%	-6%	7%
AFO_group (Unaided)	11% ± 10%	19% ± 3%	6% ± 6%	15% ± 12%	6% ± 6%	14% ± 11%	11% ± 9%
AFO_group (Aided)	10% ± 4%	13% ± 5%	4% ± 3%	9% ± 4%	4% ± 1%	9% ± 3%	9% ± 3%

*Case study participant who completed three sessions separated by several weeks.
**Group mean is the average of |individual values|

Table 7.13: Variability within pwMS's Symmetry Parameters

Participant / Parameter	Step Length		Step Time		Stance Time		Swing Time		Stance		Swing		Single Support	
	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg
AFO-user_01* (Unaided)	13%	14%	9%	6%	8%	8%	7%	6%	2%	2%	4%	4%	5%	4%
AFO-user_01* (Ottobock)	11%	9%	7%	4%	6%	6%	7%	3%	2%	2%	4%	4%	4%	4%
AFO-user_02 (Unaided)	25%	23%	9%	5%	8%	8%	12%	17%	4%	6%	11%	19%	4%	9%
AFO-user_02 (Ottobock)	11%	25%	11%	23%	6%	17%	19%	55%	6%	16%	13%	44%	13%	20%
AFO-user_03 (Unaided)	9%	25%	14%	16%	12%	11%	15%	23%	9%	9%	14%	21%	17%	20%
AFO-user_03 (Ottobock)	9%	8%	11%	14%	11%	8%	11%	6%	7%	3%	12%	5%	7%	16%
AFO-user_04* (Hinged)	5%	12%	7%	6%	6%	6%	6%	6%	2%	3%	4%	5%	5%	3%
FES-user_01* (WalkAide)	7%	8%	7%	5%	7%	8%	6%	6%	2%	2%	4%	4%	3%	3%
AFO_group (Unaided mean)	16%	21%	11%	9%	9%	9%	11%	15%	5%	6%	10%	15%	8%	11%
AFO_group (Aided mean)	9%	12%	9%	10%	7%	9%	10%	15%	4%	5%	7%	12%	7%	9%

*Case study participant who completed three sessions separated by several weeks.

7.2.2.4 Qualitative Parameters

Table 7.12 summarizes participants' RPE and walking confidence scores for both aided and unaided trials. Higher RPE values represent higher amounts of perceived exertion during trials, while lower walking confidence scores represent higher confidence during ambulation. For the unaided trials, two pwMS rated their RPE at 15 ('hard') and one rated hers at 9 ('very light'). As a group, pwMS averaged an RPE of 13 ('somewhat hard') for unaided walking trials. For the aided trials, the AFO-user group averaged an RPE score of 12 (between 'light' and 'somewhat hard'). Two participants lowered their RPE score by one: AFO-user_02 rated her RPE as 14 (between 'somewhat hard' and 'hard') and AFO-user_03 rated hers as 8 (between 'extremely light' and 'very light'). As AFO-user_01, the case study participant gave her Ottobock assisted trial an RPE of 15, which was the same as her unaided rating. While using her hinged AFO as AFO-user_04, she ranked her RPE as a 12, which was three scores below her unaided trial. Lastly, as FES-user_01, the case study's RPE score was a 14, just one score below her unaided trial.

For unaided trials, pwMS averaged a walking confidence score of 3 ('somewhat confident'). Two pwMS rated their confidence as 3 while one rated hers as 4 ('neutral – neither confident nor unconfident'). For aided trials, the AFO-user group also averaged a 3 for walking confidence. The confidence scores of both AFO-user_03 and AFO-user_04 remained at 3. But the confidence scores of both AFO-user_01 and AFO-user_02 improved by one during aided trials. AFO-user_01's aided confidence was a 2 ('confident') versus her unaided rating of 'somewhat confident.' AFO-user_02's aided confidence was 'somewhat confident' versus her unaided rating of 'neutral.' Lastly, as FES-user_01, the case study participant improved her confidence score by one, changing her unaided rating of 'somewhat confident' to 'confident' with the use of her WalkAide.

Table 7.14: Qualitative Questionnaire Results for pwMS

Participant	Borg 6-20 RPE		Walking Confidence	
	Unaided Trial	Aided Trial	Unaided Trial	Aided Trial
AFO-user_01*	15	15	3	2
AFO-user_04*		12		3
FES-user_01*		14		2
AFO-user_02	15	14	4	3
AFO-user_03	9	8	3	3
AFO_group	13 ± 3	12 ± 3	3 ± 1	3 ± 1

*Case study participant who completed three sessions separated by several weeks and used an Ottobock AFO, hinged AFO, and WalkAide.

7.2.2.5 Orthotic Gait

The effects of participant's foot-drop devices were explored by calculating the differences and percent differences between their aided and unaided walking trial results. Unaided trials were used as the baselines for all calculations. Orthotic effects for all mobility and gait symmetry parameters are provided in the following pages. Table 7.13 provides the differences between MS participant's aided and unaided trials, where negative signs indicate that unaided trials had higher values than aided trials. All pwMS saw improvements in their walking speeds regardless of the type of foot-drop device they used. Although everyone experienced improved speed, two participants had increases in their cadence: AFO-users 02 and 03. The case study participant experienced decreases in her cadence for all three of her aided sessions. For step width, AFO-user_03 had no change while everyone else's decreased. For both step and stride lengths, every participant had larger values during their aided trials than during their unaided trials. For both step and stride times, AFO-users 02 and 03 had smaller aided values than unaided. The case study participant, on the other hand, experienced increases in both of these

parameters for each of her aided trials except for step time as AFO-user_01 where she had no change. There were mixed results for both stance time and swing time. For stance time, all AFO-users had higher unaided times except for AFO-user_01, who had a slightly higher aided time. FES-user_01 also had a higher aided stance time than unaided. For swing time, the following participants had higher aided swing times than unaided: AFO-users 02 and 04 and FES-user_01. AFO-user_03 had a higher unaided swing time than her aided trial, and AFO-user_01 experienced no change. All participants, regardless of the foot-drop device used, had a higher percentage of time spent in (1) single leg support during their aided trials and (2) total double support during unaided trials.

Table 7.15: Orthotic Effects of Devices on Mobility Parameters

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
AFO-user_01* (Ottobock)	+0.04	-2	-0.01	+0.02	+0.04	0.00	+0.01	+0.01	0.00	+0.12	-0.17
AFO-user_02 (Ottobock)	+0.24	+3	-0.03	+0.12	+0.23	-0.01	-0.09	-0.11	+0.03	+0.45	-4.66
AFO-user_03 (Ottobock)	+0.17	+4	0.00	+0.06	+1.13	-0.02	-0.04	-0.03	-0.01	+1.12	-1.52
AFO-user_04* (Hinged)	+0.21	-2	-0.03	+0.10	+0.21	+0.01	+0.01	-0.01	+0.01	+1.23	-2.56
FES-user_01* (WalkAide)	+0.14	-7	-0.04	+0.09	+0.19	+0.03	+0.06	+0.04	+0.02	+0.43	-0.85
AFO_group	+0.17 ± 0.09	+1 ± 3	-0.02 ± 0.02	+0.08 ± 0.04	+0.40 ± 0.49	-0.01 ± 0.01	-0.03 ± 0.05	-0.04 ± 0.05	+0.01 ± 0.02	+0.73 ± 0.53	-2.23 ± 1.89

*Case study participant who completed three sessions separated by several weeks.

Table 7.14 provides the percent differences between MS participant's aided and unaided trials, where negative signs indicate that unaided trials had higher values than aided trials. The AFO-user group experienced an average increase in walking speed of 23% with only a 1% increase in cadence. While the AFO-user group had a decrease in step width by 11%, both their average step and stride lengths increased by 19%. As a group, AFO-users experienced decreases in step, stride, and stance times by 1%, 2%, and 4%, respectively. The AFO-user group also increased their swing time by 3% and percentage of time spent in single leg support by 2%. Lastly, the AFO-user group's average percentage of time spent in total double support decreased by 6%.

Table 7.16: Percent Orthotic Effects on Mobility Parameters

Participant	Walking Speed	Cadence	Step Width	Step Length	Stride Length	Step Time	Stride Time	Stance Time	Swing Time	Single Support (total per leg)	Total Double Support
AFO-user_01* (Ottobock)	4%	-1%	-8%	5%	5%	0%	1%	2%	0%	0%	0%
AFO-user_02 (Ottobock)	50%	3%	-14%	39%	37%	-2%	-7%	-12%	10%	2%	-9%
AFO-user_03 (Ottobock)	16%	4%	0%	10%	706%	-4%	-4%	-4%	-3%	3%	-5%
AFO-user_04* (Hinged)	23%	-1%	-23%	23%	24%	2%	1%	-2%	3%	4%	-7%
FES-user_01* (WalkAide)	15%	-5%	-31%	20%	22%	6%	6%	6%	6%	1%	-2%
AFO_group	23% ± 19%	1% ± 3%	-11% ± 10%	19% ± 15%	19% ± 342%	-1% ± 2%	-2% ± 4%	-4% ± 6%	3% ± 5%	2% ± 2%	-6% ± 4%

*Case study participant who completed three sessions separated by several weeks.

Tables 7.15 and 7.16 present the orthotic effects of devices for the gait symmetry parameters provided in Table J.4. The first table provides the differences between aided and unaided trials while the second provides the percent differences, which illustrates the magnitude of orthotic effects for each participant. Table 7.15 shows that all foot-drop devices generated increases in step length for both the right and left legs. While three of the aided trials created nearly identical increases in step length, AFO-users 03 and 04 had nearly double the difference in one leg versus the other. For step time, all of the case study's aided trials either produced no change over her unaided trial or increased her time. AFO-user_02 experienced mixed results. Use of her AFO decreased her left leg's step time while simultaneously increasing her right leg's time. Similarly, AFO-user_03 saw no change in her step time for her right leg, but use of her AFO decreased her left leg's time. For stance time, device usage caused increases or no change for the case study participant's Ottobock and FES trials; but her hinged AFO caused no change and a decrease in stance time. AFO-users 02 and 03 experienced decreases in both their left and right legs' stance times with the use of their devices. Use of a foot-drop device caused an increase in swing time for both legs of all participants except for AFO-user_01's left leg, which had no change, and AFO-user_03's left leg, which had a decrease in swing time with the same magnitude of change as her right leg. The orthotic effects of devices on percentages of time spent in stance, swing, and single support were mixed. For percentage of time spent in stance, AFO-users 02 and 04 had decreases in both of their legs while FES-user_01 and AFO-users 01 and 03 experienced increases in their left legs and decreases in their right legs. For percentage of time spent in the swing phase of the gait cycle, AFO-users 02 and 04 experienced increases in both of their legs while FES-user_01 and AFO-users 01 and 03 experienced decreases in their left legs and increases in their

right legs. Finally, for the percentage of time spent in single support, AFO-user_04 and FES-user_01 experienced increases in both their legs, AFO-users 01 and 03 had increases in their left legs and decreases in their right, and AFO-user_02 had a decrease in her left leg and increase in her right.

Table 7.16 illustrates that AFOs produced an average increase in step length of 20% for the right leg and 18% for the left. Changes in step time for the AFO-user group was mixed. On average, they experienced a 4% decrease in step time for their left leg and a 1% increase for their right. The AFO-user group decreased their stance times by 3% for their left leg and 5% for their right; but for swing time, AFO-users averaged a 1% increase for the left leg and 8% increase for the right. Based on the average percentage of time spent in stance, AFOs decreased wearers' overall time spent in stance by 1% for the left leg and 3% for the right. The AFO-user group also experienced an overall increase in percentage of time spent in the swing phase of the gate cycle for both legs. The left leg increased by 3% while the right increased by 9%. Lastly, although the AFO-user group's average percentage of time spent in single support increased by 4% for their left leg, AFOs caused no change in the right leg for the group.

Table 7.17 summarizes the orthotic effects of devices on degree of asymmetry. This was calculated by subtracting the absolute value of aided trials from the absolute value of unaided trials. This allowed negative signs to indicate that devices decreased the degree of asymmetry. The values of Table 7.10 were used to calculate these effects. Each pwMS experienced their own patterns of improved and worsened symmetry for the examined parameters. Some participants experienced improved symmetry while the use of an AFO significantly worsened several symmetry parameters. On average, the AFO group experienced worsened degrees of asymmetry when devices were used.

Table 7.17: Orthotic Effects of Devices on Symmetry Parameters

Participant / Parameter	Step Length (m)		Step Time (s)		Stance Time (s)		Swing Time (s)		Stance %		Swing %		Single Support %	
	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg
AFO-user_01* (Ottobock)	+0.02	+0.02	+0.01	0.00	+0.01	0.00	0.00	+0.01	+0.21	-0.32	-0.21	+0.32	+0.36	-0.15
AFO-user_02 (Ottobock)	0.13	+0.10	-0.06	+0.01	-0.11	-0.13	+0.03	+0.02	-4.09	-3.70	+4.09	+3.70	-0.39	+1.39
AFO-user_03 (Ottobock)	+0.04	+0.10	-0.05	0.00	-0.01	-0.05	-0.04	+0.04	+1.66	-3.70	-1.66	+3.70	+2.98	-1.83
AFO-user_04* (Hinged)	+0.13	+0.07	0.00	+0.01	0.00	-0.01	+0.01	+0.03	-0.49	-2.16	+0.49	+2.16	+2.25	+0.20
FES-user_01* (WalkAide)	+0.11	+0.08	+0.02	+0.04	+0.04	+0.02	+0.02	+0.03	+0.03	-0.92	-0.03	+0.92	+0.72	+0.70
AFO_group	+0.08 ± 0.06	+0.07 ± 0.04	-0.03 ± 0.04	+0.01 ± 0.01	-0.03 ± 0.06	-0.05 ± 0.06	0.00 ± 0.03	+0.03 ± 0.01	-0.68 ± 2.44	-2.47 ± 1.61	+0.68 ± 2.44	+2.47 ± 1.61	+1.30 ± 1.58	-0.10 ± 1.33

*Case study participant who completed three sessions separated by several weeks.

Table 7.18: Percent Orthotic Effects of Devices on Symmetry Parameters

Participant / Parameter	Step Length		Step Time		Stance Time		Swing Time		Stance		Swing		Single Support	
	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg
AFO-user_01* (Ottobock)	4%	5%	2%	0%	2%	0%	0%	3%	0%	0%	-1%	1%	1%	0%
AFO-user_02 (Ottobock)	41%	33%	-9%	2%	-12%	-13%	9%	7%	-6%	-5%	16%	16%	-2%	5%
AFO-user_03 (Ottobock)	6%	20%	-8%	0%	-1%	-7%	-10%	13%	3%	-5%	-4%	13%	10%	-5%
AFO-user_04* (Hinged)	29%	16%	0%	2%	0%	-2%	3%	10%	-1%	-3%	2%	6%	7%	1%
FES-user_01* (WalkAide)	24%	19%	5%	8%	6%	3%	7%	10%	0%	-1%	0%	3%	2%	0%
AFO_group	20% ± 18%	18% ± 12%	-4% ± 6%	1% ± 1%	-3% ± 6%	-5% ± 5%	1% ± 8%	8% ± 4%	-1% ± 3%	-3% ± 2%	3% ± 9%	9% ± 7%	4% ± 5%	0% ± 4%

*Case study participant who completed three sessions separated by several weeks.

Table 7.19: Orthotic Effects of Devices on Degree of Asymmetry

Participant	Step Length	Step Time	Stance Time	Swing Time	Stance	Swing	Single Support
AFO-user_01* (Ottobock)	-1%	-2%	2%	3%	1%	2%	1%
AFO-user_02 (Ottobock)	6%	-11%	-1%	2%	1%	0%	7%
AFO-user_03 (Ottobock)	-12%	-9%	-6%	-19%	-8%	-17%	-14%
AFO-user_04* (Hinged)	10%	2%	2%	6%	3%	5%	6%
FES-user_01* (WalkAide)	4%	3%	3%	3%	2%	3%	2%
AFO_group	0.75%	-5%	-1.75%	-2%	-0.75%	-2.50%	0%

*Case study participant who completed three sessions separated by several weeks.

7.2.2.6 Flat Ground Multimodal Trial Segments

Since this dissertation's experimental setup is novel compared to most MS-related gait studies, comparing trial results against segments that have a consistent pitch of zero degrees is useful. The treadmills remained level for the first thirteen meters of every trial and included targets after the first few meters. The author reviewed session footage for each walking trial to determine when participants reached a consistent gait pattern. At the beginning of every trial, it took all pwMS around ten-to-fourteen seconds to get used to the self-paced mode, so those steps were omitted for analysis. Selected gait cycles began from the point of consistent gait and terminated within a few steps of the first change in pitch. A minimum of seven complete left and right gait cycles were included in the GOAT analysis for the flat ground multimodal results. The overall mobility parameters (averages and standard deviations) for these flat ground trial segments are summarized in the Table 7.18 below. Table 7.19 presents the differences between flat ground walking and the full

multimodal walking trials for both aided and unaided walking conditions. Differences were calculated so that negative signs indicate that the flat ground segment average was lower than the full multimodal walking trial average.

Every aided and unaided trial completed on the flat ground segment had slower walking speeds than those on the full multimodal trials except for AFO-user_02's unaided trial. During the flat ground segment, three trials had higher cadence while the rest had fewer steps when compared to the full multimodal trials. Step width was unchanged for three trials; but for the rest of the trials, participants had larger widths between their steps during flat ground walking than the full multimodal trial. Only two trials had longer step and stride lengths during the flat ground segment while the rest were shorter than those seen during the full multimodal trials. Across all four of the time-domain parameters, there were four instances of zero change between the flat segments and full multimodal trials, and only five instances of the flat ground walking resulting in lower times than the full trials. Finally, walking during the flat ground segment resulted in lower percentages of time spent in single support for most of the trials while causing higher percentages of time in double support for most of the trials when compared to the full multimodal trial.

7.3 Observations and Participant Feedback

The following are observational notes taken by the PI during sessions and relevant participant feedback and commentary. Participants developed different techniques and strategies for hitting oncoming targets during their multimodal walking trials. Some performed slow, controlled swiping motions with one arm while others waved both hands frantically. One participant even chose to chain punch at oncoming targets. Participants often experimented with different methods of hitting targets during their acclimation trials and, either consciously or unconsciously, tended to stick with one method during

their multimodal trials. Overall, participants preferred arm motions that travelled away from their bodies and faces. In preparation for hitting a target, they often moved one hand close to their midline about chest height. Then as the target came into hitting range, they would move their hand distally. Some participants relied on one arm to hit targets that approached from both their left and right sides instead of alternating arms.

Table 7.20: Flat Ground Multimodal Trial Results

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
AFO-user_01* (Unaided)	0.78 ± 0.09	118 ± 10	0.15 ± 0.02	0.40 ± 0.03	0.80 ± 0.05	0.51 ± 0.04	1.02 ± 0.05	0.69 ± 0.04	0.33 ± 0.02	32.17 ± 1.46	35.60 ± 2.06
AFO-user_01* (Ottobock)	0.90 ± 0.10	121 ± 9	0.13 ± 0.02	0.45 ± 0.02	0.90 ± 0.04	0.50 ± 0.04	1.00 ± 0.04	0.67 ± 0.04	0.33 ± 0.02	32.77 ± 1.84	34.58 ± 1.60
AFO-user_02 (Unaided)	0.54 ± 0.09	106 ± 39	0.23 ± 0.02	0.33 ± 0.03	0.66 ± 0.03	0.61 ± 0.15	1.22 ± 0.13	0.87 ± 0.10	0.34 ± 0.10	27.30 ± 10.30	40.66 ± 11.94
AFO-user_02 (Ottobock)	0.61 ± 0.17	106 ± 16	0.21 ± 0.03	0.35 ± 0.08	0.69 ± 0.15	0.58 ± 0.08	1.16 ± 0.07	0.85 ± 0.07	0.31 ± 0.07	26.45 ± 4.50	47.09 ± 4.93
AFO-user_03 (Unaided)	1.01 ± 0.20	126 ± 82	0.08 ± 0.01	0.62 ± 0.06	1.22 ± 0.09	0.59 ± 0.22	1.19 ± 0.14	0.77 ± 0.19	0.43 ± 0.17	33.50 ± 18.39	25.70 ± 12.86
AFO-user_03 (Ottobock)	1.16 ± 0.19	112 ± 8	0.08 ± 0.01	0.64 ± 0.04	1.28 ± 0.05	0.54 ± 0.04	1.08 ± 0.06	0.73 ± 0.06	0.35 ± 0.02	33.07 ± 1.86	34.29 ± 2.19
AFO-user_04* (Hinged)	0.94 ± 0.17	123 ± 14	0.10 ± 0.03	0.48 ± 0.07	0.95 ± 0.10	0.50 ± 0.06	0.99 ± 0.06	0.66 ± 0.05	0.33 ± 0.02	33.12 ± 2.13	33.57 ± 231
FES-user_01* (WalkAide)	0.97 ± 0.14	121 ± 15	0.10 ± 0.03	0.50 ± 0.05	0.99 ± 0.09	0.50 ± 0.06	1.02 ± 0.05	0.68 ± 0.04	0.33 ± 0.02	33.12 ± 1.88	33.95 ± 2.47
AFO_group (Unaided)	0.78 ± 0.24	117 ± 10	0.15 ± 0.08	0.45 ± 0.15	0.89 ± 0.29	0.57 ± 0.05	1.14 ± 0.11	0.78 ± 0.09	0.37 ± 0.06	30.99 ± 3.26	33.99 ± 7.61
AFO_group (Aided)	0.90 ± 0.23	116 ± 8	0.13 ± 0.06	0.48 ± 0.12	0.48 ± 0.12	0.96 ± 0.24	0.53 ± 0.04	1.06 ± 0.08	0.33 ± 0.02	31.35 ± 3.27	37.38 ± 6.49

*Case study participant who completed three sessions separated by several weeks.

Table 7.21: Difference between Flat Segment and Full Multimodal Trials

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
AFO-user_01* (Unaided)	-0.15	-12	0.02	-0.04	-0.07	0.04	0.08	0.06	0.02	-0.61	1.25
AFO-user_01* (Ottobock)	-0.07	-7	0.01	-0.01	-0.01	0.03	0.05	0.03	0.02	-0.13	0.40
AFO-user_02 (Unaided)	0.06	6	0.01	0.02	0.04	0.00	-0.03	-0.07	0.03	1.34	-8.76
AFO-user_02 (Ottobock)	-0.11	3	0.02	-0.08	-0.16	-0.02	0.00	0.02	-0.03	0.04	2.33
AFO-user_03 (Unaided)	-0.03	14	0.00	0.03	1.06	0.04	0.11	0.06	0.06	-0.40	-6.09
AFO-user_03 (Ottobock)	-0.05	-4	0.00	-0.01	-0.01	0.01	0.04	0.05	-0.01	-1.95	4.02
AFO-user_04* (Hinged)	-0.20	-5	0.00	-0.06	-0.13	0.02	0.04	0.04	0.01	-0.89	1.78
FES-user_01* (WalkAide)	-0.10	-1	0.01	-0.03	-0.07	0.00	0.02	0.01	0.00	-0.09	0.45
AFO_group (Unaided)	-0.04	3	0.01	0.00	0.34	0.03	0.05	0.02	0.04	0.11	-4.53
AFO_group (Aided)	-0.11	-3	0.01	-0.04	-0.08	0.01	0.03	0.04	0.00	-0.74	2.13

*Case study participant who completed three sessions separated by several weeks.
**Averages of full multimodal segments were subtracted from flat ground segment averages.

During most trials, the PI had to remind participants to walk at their normal, comfortable paces because they became too preoccupied with hitting targets – which was not their primary objective. Verbal reminders occurred if participants did one of the following: continuously held their arms in a 'ready stance' between chest and head height, continuously waved their arms when targets were not within hitting range, notably slowed

down as targets approached, or walked faster and more aggressively than usual if they missed a few targets. Some participants became quite frustrated or embarrassed by missing targets; some vented their frustrations with 'tsk' sounds, sighs, and/or verbally with self-criticism, various exclamations, and even cursing.

While completing walking trials, participants rarely maintained a 'straight line' on the treadmill. Each tended to drift left and right across the width of the treadmill throughout their trials. This meant that the left and right foot frequently crossed the midline between the treadmill belts. The belts moved in unison during trials, so crossing the line did not inhibit participants' gait; however, drifting across the belts negated the benefit of having dedicated left and right force plates. Some participants found the virtual reality experience of CAREN a bit jarring, but they adapted during their acclimation trials. This was true for persons who had little-to-no exposure to virtual reality systems or who rarely used treadmills. Although some participants held onto the handrails or stumbled occasionally, there were no falls or significant trips during trials.

7.3.1 The Control Group

Most controls had little experience with virtual reality systems or treadmills, which matched the experiences of participants with MS. Three controls had situational variables that could have impacted their walking performances. First is control_09, who had to be constantly reminded to focus on walking normally because she became too preoccupied with hitting targets and exploring the immersive simulation visuals. When targets appeared on the screen, she tended to alter her gait by walking notably faster and continuously undulating her arms until targets passed out of range. All participants scanned the projected scenery, but control_09 used a larger range of head motions than most other participants. Her larger motions may have caused her some disorientation

because she periodically bumped into the handrails and even reached the harness's tether limit a few times. Lastly, the way she navigated the changes in floor pitch allowed her to barrel through them. She adopted a bouncy gait with more springiness in her knees but heavier footfalls from heel-to-toe that often slapped the toes loudly on the ground. The second participant worth noting is control_12, who was particularly accustomed to both virtual reality systems and treadmills. She owned an Oculus virtual reality system, was an avid player, and placed in Beat Saber competitions. She had also been training to hike the Appalachian trail for a few months, which entailed daily treadmill sessions lasting 3-4 hours with extreme incline settings and a weighted pack. The last participant of note was control_13, whose height was near the limit of what CAREN could support. He was the tallest participant at 1.93-meters (6-foot 3-inches). He could not physically stand in the center of CAREN's platform like the rest of the participants because the harness suspension frame was both too short and too narrow for him to comfortably and safely clear. While standing upright in the center of the platform, his head could almost touch the harness's attachment point on the frame and his arm span was limited by the frame's anchoring bars. Placing him approximately 0.30-meter (1-foot) ahead of the center point of the platform addressed these issues and provided a comfortable amount of clearance for both his head and arms. Unfortunately, this shortened the distance he could move forward on the treadmill and meant that he often reached the harness tether limit. He had naturally long strides, so feeling like he was so close to the edge of the treadmill and platform may have mentally limited his walking behaviors. Lastly, CAREN sometimes struggled with smoothly tracking his hand markers since his arm span could extend outside the of the typical capture volume the PI calibrated within. Although this didn't disrupt data collection, it did hinder his ability to consistently hit targets.

7.3.2 Participants with Multiple Sclerosis

Every participant with MS took their first step with their sound leg at the beginning of both their aided and unaided walking trials. Each participant commented on how burdensome and time consuming it was for them to don and doff their AFOs. Firstly, AFOs require a degree of strength and dexterity to properly situate them into footwear (which is often a very snug fit) and to comfortably relace the shoe. Although shoes with hook-and-loop closures could assist with this, the selection is limited and all three pwMS found them unattractive and overall undesirable. Secondly, insoles must be removed from shoes while using AFOs, but pwMS need the insoles when AFOs are not being used. Participants found constantly removing and replacing insoles frustrating and highlighted the hassles of stowing their insoles:

- "It's just one more thing I have to keep track of. If I lose the insole, I can't wear these shoes anymore. I'd either have to buy new shoes or get new insoles, which is expensive either way."
- "I don't always wear my AFO, but if I travel, I have to take it with me. The AFO is bulky on its own, but it's also tricky to store my shoe insole. The insole has to be securely and inconspicuously stored so I don't lose it and other people can't see it. Insoles are gross and dirty, so I don't want to just toss in my purse either."

Although duplicate or dedicated shoes for use with and without their AFOs could help with these frustrations, participants found the extra expense and possibility of grabbing the wrong pair of shoes quite off-putting. Lastly, using AFOs for prolonged periods of time caused general discomforts. All participants complained that their AFOs trapped a lot of heat. Excess heat is uncomfortable in general, but pwMS are heat sensitive and it can also trigger their fatigue. The heat also made wearers sweat a lot, causing both their shoes and

AFOs to become odorous. Lastly, the contact points between AFOs and their wearers can become uncomfortable with extended use due to rubbing and pressure.

All pwMS emphatically expressed disappointment with their limited footwear options. Having foot-drop imposed general footwear limitations and AFO requirements narrowed options further. All pwMS purposely scheduled their sessions around mid-morning for two reasons: (1) to avoid heavy traffic, which reduced stress, anxiety, and the amount of cognitive effort required to drive alertly and defensively and (2) to capitalize on their higher morning energy levels. All three participants stated that they had the most energy in the morning and could become fatigued by the afternoon. They all made use of energy conservation strategies whenever they planned more strenuous activities. Lastly, all pwMS noted fatigue, heat sensitivity, foot-drop, and imbalance as the primary inhibitors to their desired physical activities and lifestyles. Each participant exhibited significant and heavily engrained compensatory motions to address foot-drop.

The building in which sessions were conducted had a locked thermostat around 73˚F but lowering the set point to the 60s would have been ideal. Many participants, controls and pwMS, commented about the room "becoming too hot" once they started their trials, and most broke into a sweat during some portion of their session. The combination of increased body temperature during ambulation and the heat CAREN generated and trapped near the platform was considerable. This was particularly concerning for pwMS since their heat sensitivity could exacerbate fatigue. The PI provided ice-cold water to help mitigate the temperature issue, but a cooler ambient temperature and a floor fan for rapid cooling would have been most beneficial.

The case study participant made an interesting comment about her walking adaptations since developing foot-drop. Whether or not she uses a foot-drop device, she

stated that, “I have to reach a faster walking pace for the motion to feel natural and sustainable – in particular for long distances. At slower speeds, it’s very difficult to keep going. It takes more effort, is uncomfortable, and feels less stable.” After this participant completed her final walking trial, the PI inquired about her overall device preferences since she owned an Ottobock AFO, hinged AFO, and WalkAide. Although she loved using her WalkAide and was pleased with its results, her body stopped responding as efficiently to transcutaneous stimulation, so wearable FES was no longer a reliable treatment option. (This happened a month or two after she completed her FES session.) She expressed a strong preference for her hinged AFO, which she had used daily for over six months. It quickly became her primary foot-drop device because it was more comfortable and easier to don and doff than her Ottobock. The movement the hinged AFO allowed and encouraged felt more natural because she could actually move her ankle and engage her dorsiflexor and calf muscles. She enjoyed using it as both an ambulatory and exercise aid.

Chapter 8: Discussion

Trial results for the control group, AFO-user group, and case study are interpreted within this chapter. At the end of sections 8.2 and 8.3, bar charts are provided for visual comparisons of gait performances between pwMS and the control group. The sessions completed by pwMS resulted in five aided trials and allowed the orthotic effects of three different foot-drop devices to be analyzed: the Ottobock carbon fiber Walk-On Flex AFO, a plastic hinged AFO, and the WalkAide FES. The multimodal walking environment used for this study proved to be challenging, yet achievable for participants with MS. All three pwMS safely completed their acclimation and multimodal walking trials with and without the use of their foot-drop devices.

8.1 The Control Group

Aside from providing a normative data set to compare to pwMS, the control group's results validated both this study's protocols and the multimodal walking environment. Participant demographics did not impact the patterns seen in walking performance or significantly alter perceptions within the control group, but parameter magnitudes naturally differed due to physical characteristics such as height and leg length. Although normative gait cycles on flat ground consist of spending 60-62% of total gait within the stance phase,[40] this control group averaged around 67% in stance. The 5-7% difference reflects the influence of the multimodal environment, which included changes in ground pitch, dual-tasking, and audiovisual distractions.

Table 7.5 reveals trends in the control group's mobility parameter variabilities. The group expressed the largest variabilities in step width and walking speed at 20% and 17%, respectively. Large variations in walking speeds were anticipated because participant's focus would be divided by audiovisual stimuli and multitasking throughout their trials: constantly adjusting to pitch changes while tracking the movements of targets and trying to hit them. The high variability in step width was a bit surprising. For both controls and pwMS, participants did not seem to index their location on the platform very often, which may have caused them to lose a degree of proprioception. They tended to keep their chins and gaze focused upwards on the projection screen and only periodically glanced at the floor. Participants may also have moved towards oncoming targets, which could have contributed to the observed wavering. The variable step width and lateral drift exhibited by controls and pwMS may be a natural consequence of ambulating within multimodal environments, but further investigation is required to confirm this. The control group's average degree of asymmetry ranged from 1-4% as shown in Table 7.6, meaning that controls maintained a high level of symmetry throughout their multimodal trials. Lastly, Table 7.8 shows that the control group felt confident in their walking capabilities during trials and perceived their required level of exertion as very light.

8.2 The AFO-user Group

Comparing the orthotic effects of AFO devices against the control group provides perspective on their impacts. AFO devices proved beneficial or problematic depending on which parameters were examined. Similar to controls, pwMS who used foot-drop devices spent around 67% of their gait cycle in stance but averaged higher values when unaided. AFOs improved the group's walking speed by 0.19 m/s, matching the control group. AFOs also decreased step width while increasing step and stride lengths. These changes imply

pwMS felt more stable with AFOs because they narrowed the distance between their feet and took longer steps. Although AFOs allowed pwMS to walk as fast as controls, they increased cadence, which worsened the already present difference between their unaided group average and controls. Furthermore, increased step frequency could be problematic for pwMS because it requires more energy and increases the opportunity for a trip or fall. Using AFOs did not change the group's swing time, but it did lower their step, stride, and stance times – where unaided averages were already lower than controls for all four parameters. AFOs improved gait patterns by simultaneously decreasing percentage of time spent in double support and increasing time in single support – bringing both group averages very close to those of the control group.

AFOs typically improved the group's symmetry as evidenced by their aided and unaided degrees of asymmetry as shown in Table 7.10 and their percent orthotic effects in Table 7.17, where negative signs indicate devices improved symmetry. AFO-users had the largest symmetry improvements in step and swing times, an increase in asymmetry for step length, and no change in symmetry for percentage of time spent in single support. Legs did not experience the same magnitude of changes and the leg affected by foot-drop did not always experience the greater change. Even with symmetry improvements, pwMS had significantly higher asymmetry when compared to controls – except for stance time and stance percentage which were 3% higher than controls. Directly comparing individual legs for the group would be misleading since two-thirds had foot-drop on their right leg.

With few exceptions, AFOs lowered the standard deviations within mobility and symmetry parameters for all pwMS. For the AFO group's mobility parameters, only percentages of time spent in single and double support saw increased variability. But for step width, walking speed, and stride length variabilities, the group's aided averages were

within 1% of the variability displayed by controls. This means that pwMS can greatly improve the consistency of their gait within multimodal environments by using AFOs. Although pwMS did not exhibit trends as strongly as controls regarding mobility variability, they did present overall trends that were similar to the control group. The magnitude of parameter variabilities and the descending order of parameters based on variability changed (1) across pwMS and (2) between an individual's aided and unaided trials. This illustrates the connection between gait consistency within a multimodal environment and an individual's overall level of disability and use of assistive devices. As listed in Table 7.9, the AFO group's largest variabilities occurred within: (1) unaided trials with stride length at 52% followed by walking speed at 24% and step width at 23% and (2) aided trials with step width at 19% and walking speed at 18%.

Table 7.12 conveys the perceptions of AFO-users. During unaided trials, AFO-users felt 'somewhat confident' in their walking capabilities and perceived their required level of effort as 'somewhat hard.' Using AFOs did not change the group's walking confidence and barely lowered their RPE as it was between 'light' and 'somewhat hard.' Compared to controls, the AFO group had similar confidence ratings but dramatically higher RPE, which simply reflects the influence of MS, foot-drop, and PDDS scores. Therefore, even though AFO devices created quantitative and clinically relevant improvements in overall ambulation, pwMS did not believe they helped enough to impact their confidence or RPE.

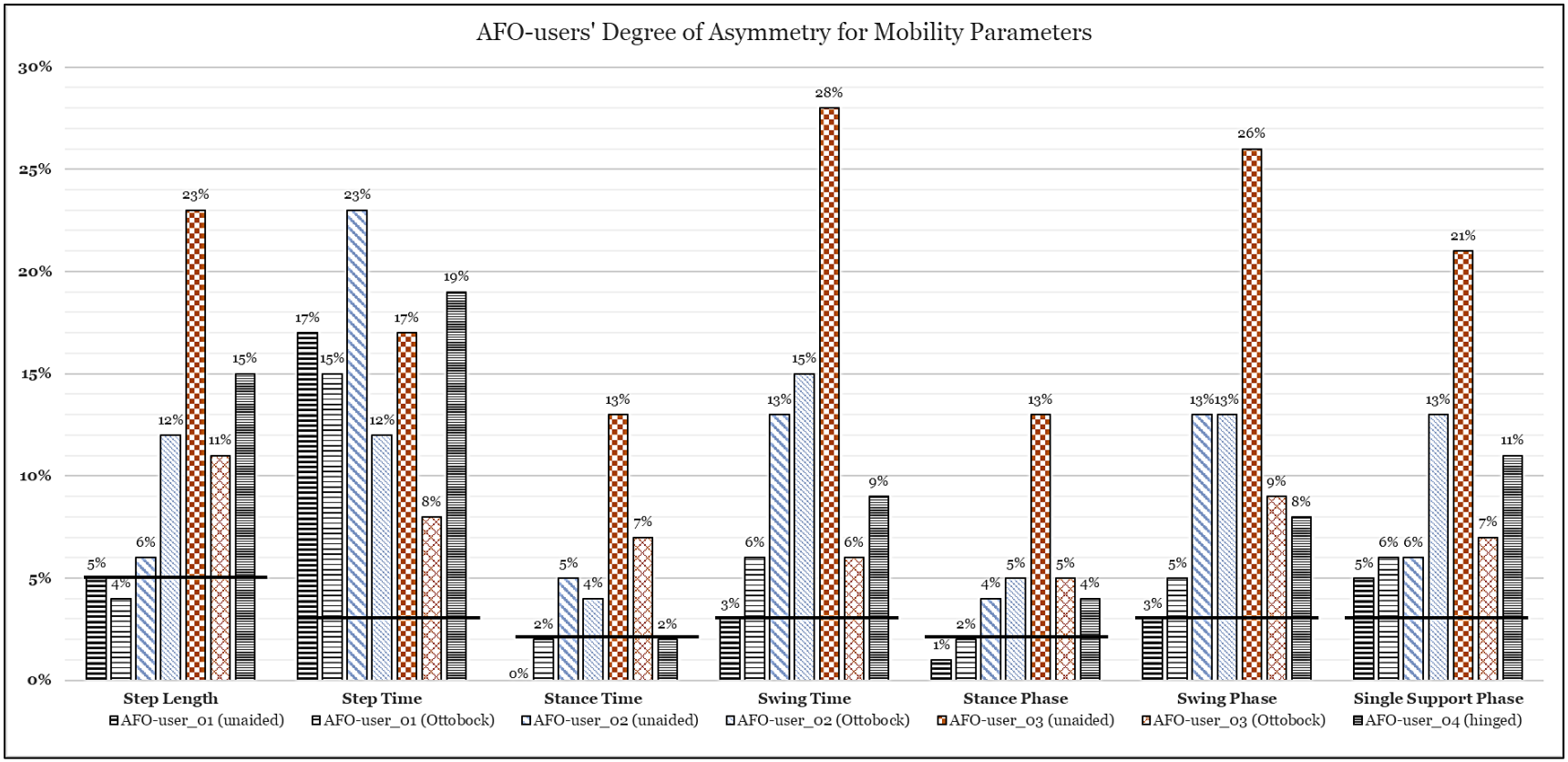

Figure 8.1: AFO-users' Degree of Asymmetry with Control Group's Average as Threshold Bar

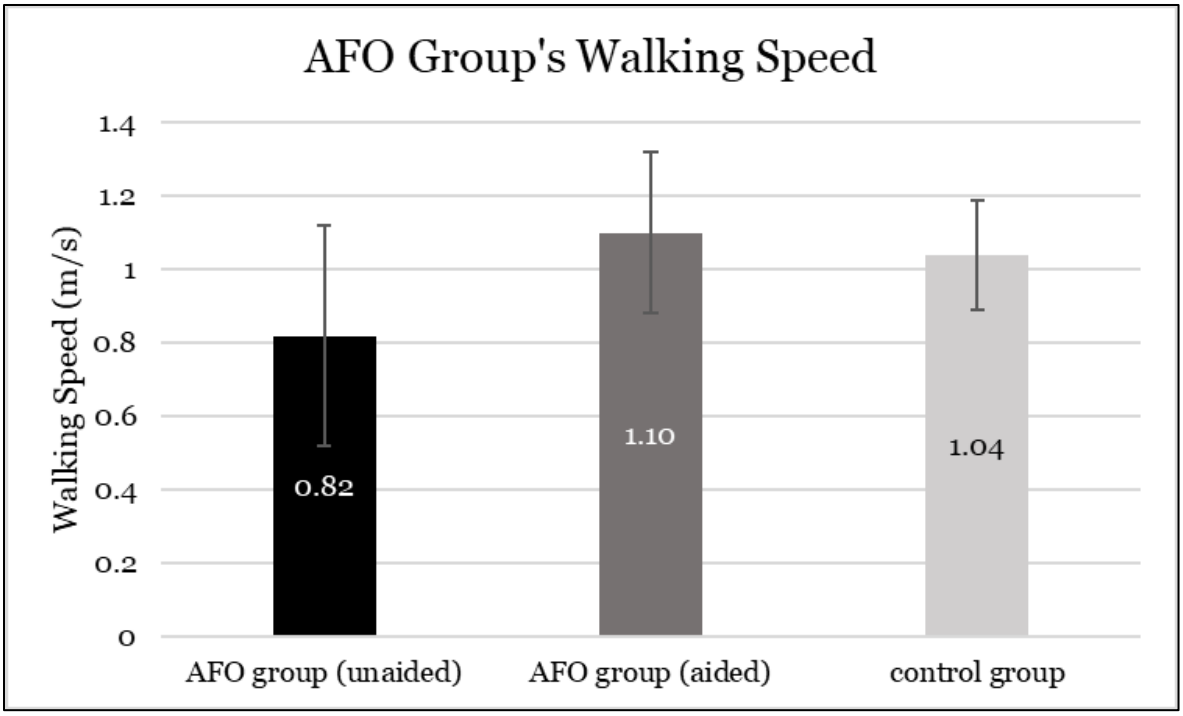

Figure 8.2: AFO Group's Walking Speed

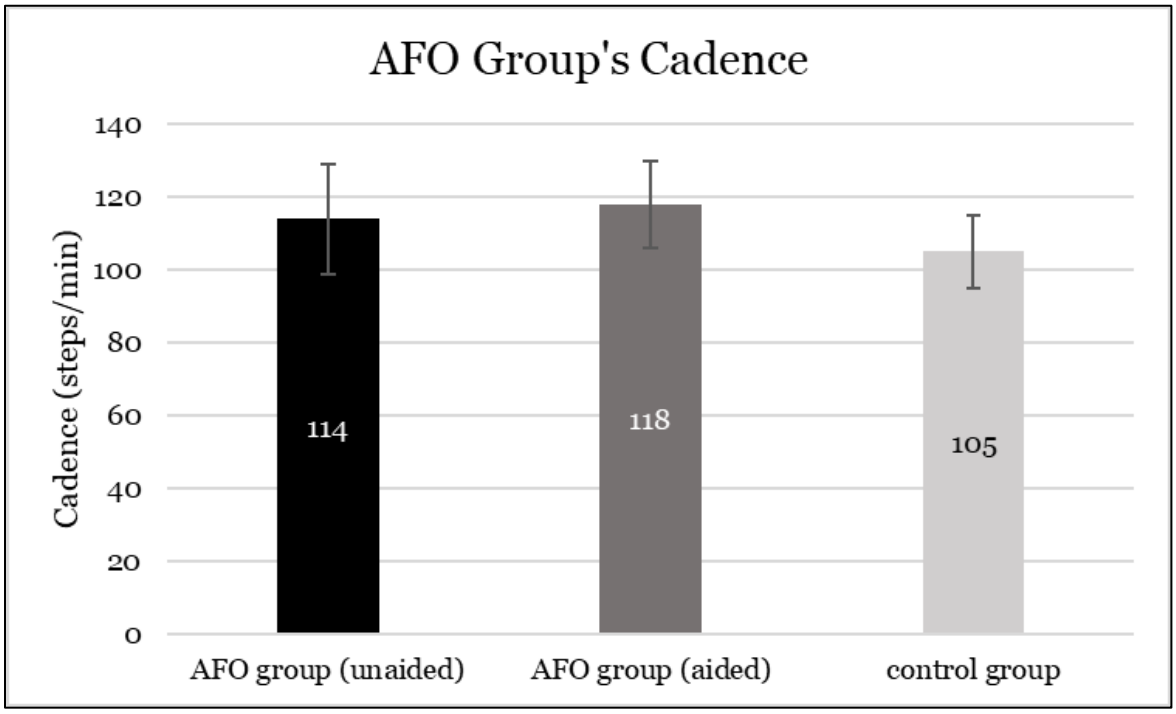

Figure 8.3: AFO Group's Cadence

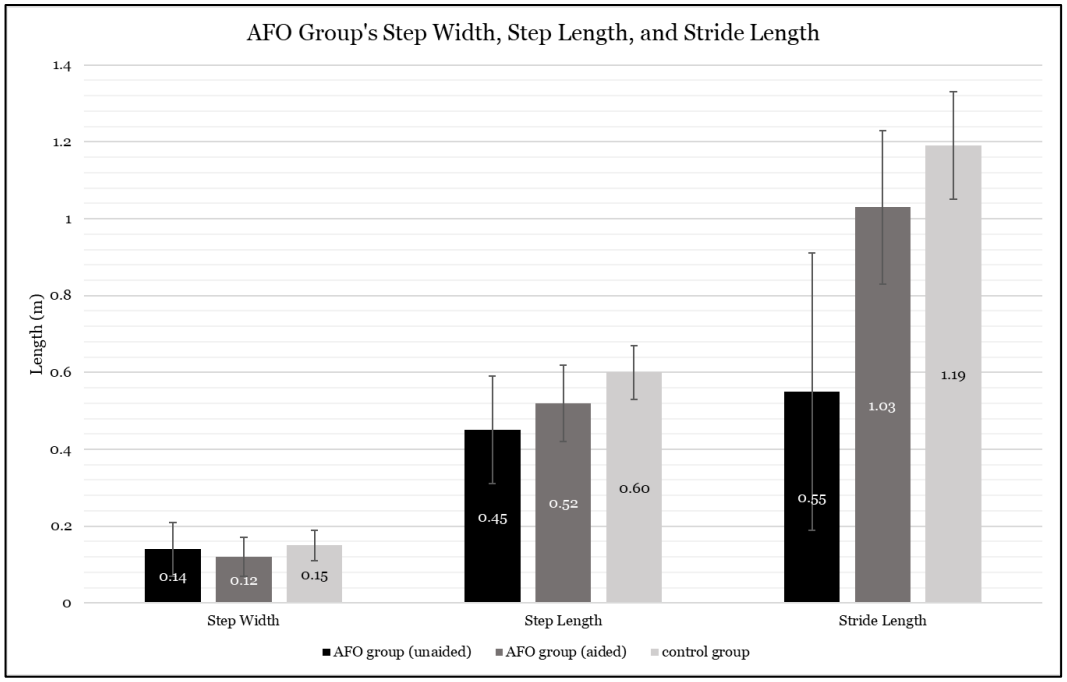

Figure 8.4: AFO Group's Step Width, Step Length, and Stride Length

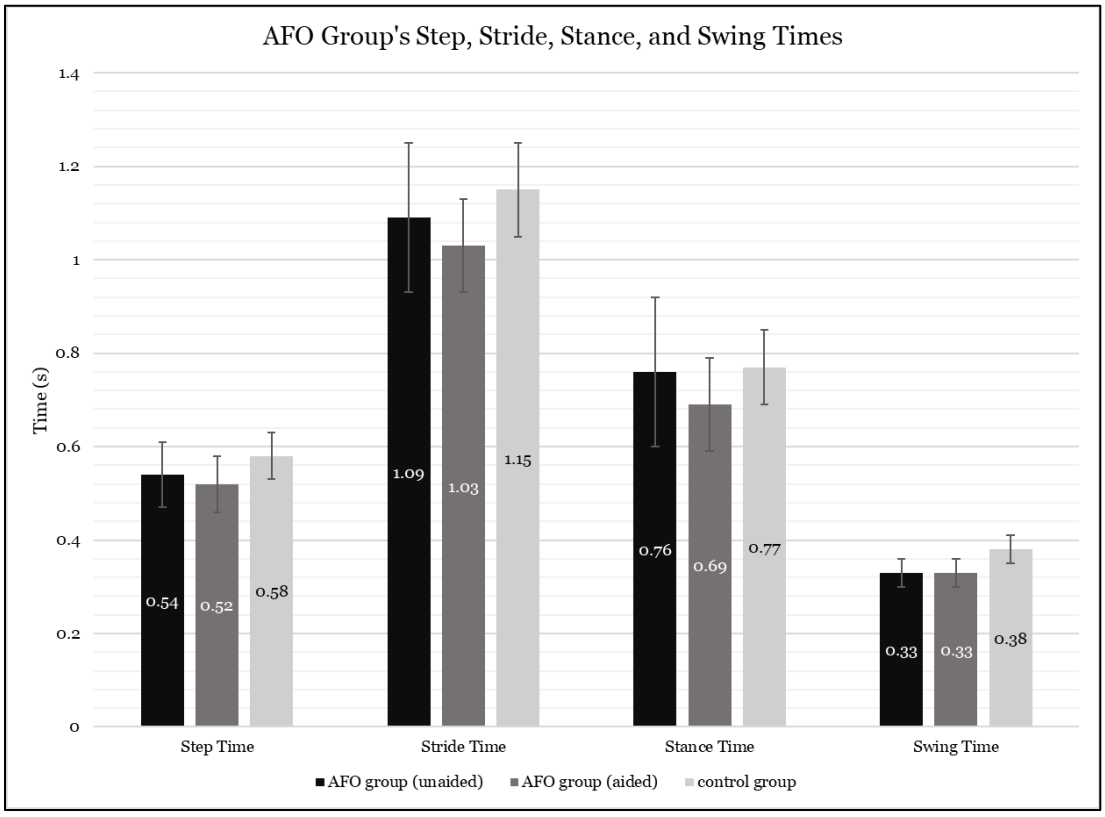

Figure 8.5: AFO Group's Step, Stride, Stance, and Swing Times

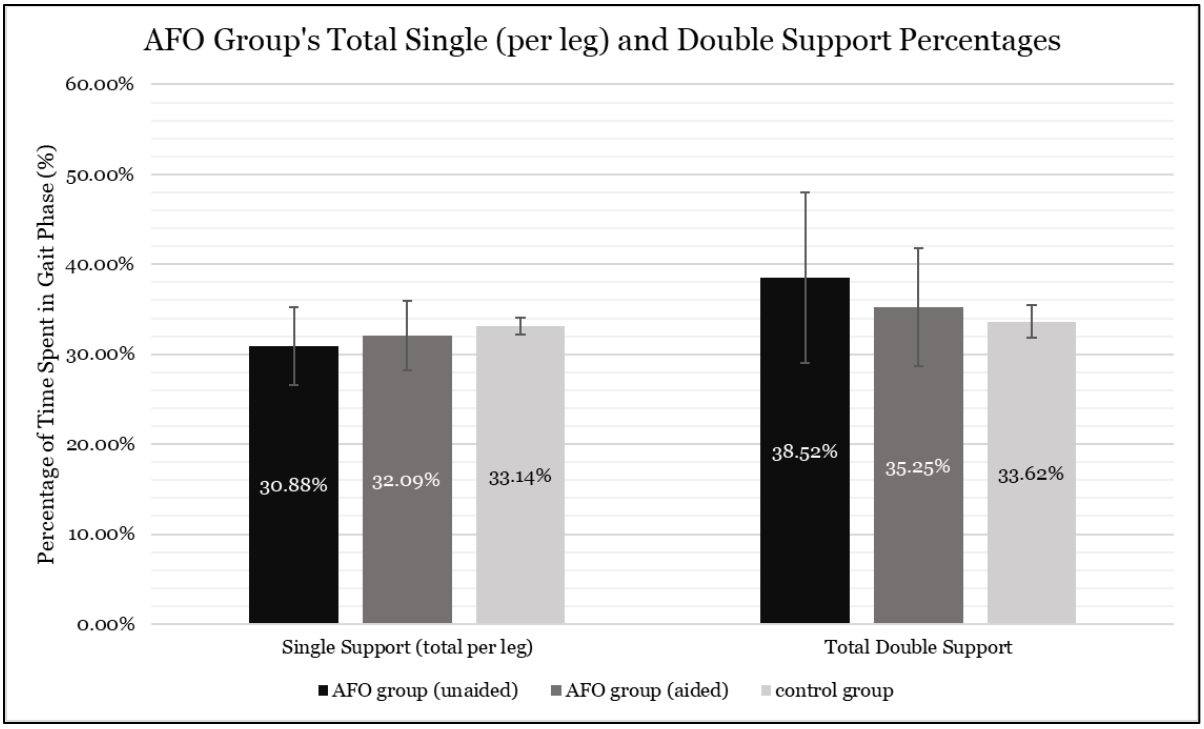

Figure 8.6: AFO Group's Single and Double Leg Support Percentages

8.3 The Case Study

The case study participant was a 58-year-old female who presented unilateral foot-drop in her right leg. She had been diagnosed with RRMS for 30 years, had a PDDS of 4, and did not use dalfampridine because of her DMT prescription. Besides foot-drop, heat sensitivity, fatigue, and imbalance were the most prominent MS symptoms that interfered with her daily activities and desired lifestyle. She owned three different foot-drop devices: a Ottobock carbon fiber Walk-On Flex AFO (10 years), a WalkAide FES (3 years), and a plastic, hinged AFO (just over 6 months). The hinged AFO was custom formed by an orthotist at a local branch of the Hanger Clinic (Hanger Clinic, Tampa FL).[41] This participant completed a total of four multimodal walking trials: one unaided and one with each device listed above. Trials were completed over three different sessions separated by

several weeks to avoid fatigue, learning, or potential user bias from affecting results. All sessions were conducted during the same time in the morning. She was randomly chosen to perform aided trials before unaided trials. She completed her unaided and Ottobock trials in the first session, the WalkAide trial in the second, and the hinged AFO trial in her third and final session. Between sessions, she had no changes in MS symptoms, symptom severity, PDDS, medications, or physical activity levels; only her weight fluctuated between two and five kilograms per session. Since there were no changes between sessions that would interfere with walking performance, her first unaided trial could be used as the baseline for all devices. Omitting unaided trials during her second and third sessions did not interfere with her aided trials since all of the aided trials were performed first. This shortened the duration of subsequent sessions and reduced the amount of time she spent on CAREN, which helped prevent learning from skewing the results of subsequent sessions. Acclimation trials were completed during every session as per the study protocol. During trials, the case study participant momentarily grasped the handrails to correct imbalance only when necessary; overall, she completed trials without relying on the handrails and attempted to hit almost all of the targets. A few months after completing her session with the WalkAide, her common peroneal nerve stopped responding as reliably to transcutaneous stimulation, so she stopped using FES to treat her foot-drop. She preferred her hinged AFO to her Ottobock and commented on it being more comfortable and easier to use than the Ottobock.

Table 8.1 lists the mobility parameter results for each of the case study's trials. Compared to her unaided trial, all three devices increased walking speed, step length, stride length, and percentage of time spent in single leg support. All three devices also decreased cadence, step width, and percentage of time spent in double support. None of

the devices generated significant changes in step, stride, stance, or swing time, and both AFOs produced nearly identical values for all those parameters. The WalkAide provided slightly higher improvements than the AFOs for step, stride, and stance times, but its effect on swing time was very similar to that of the AFOs. Comparing the orthotic effects of devices better illustrates their impacts on gait. Table 8.2 provides the orthotic effects, where positive values indicate that devices increased a parameter's value from baseline. All three foot-drop devices decreased the participant's cadence and time spent in the double support phase of the gait cycle. All three devices also increased the participant's walking speed by improving her balance as evidenced by her reduced step width, longer step length, and higher percentage of time spent in single support. Comparing the mobility effects of devices against each other and the control group reveals that the Ottobock provided the least overall benefit, the hinged AFO created the fastest walking speed, and the WalkAide produced the most parameters with values near those of controls. The Ottobock produced the smallest changes in mobility parameters when compared to the hinged AFO and WalkAide. This was true for all parameters except for step and swing times, which it had no effect on. However, the orthotic differences between the Ottobock and hinged AFOs were negligible for cadence and step, stride, and swing times. The hinged AFO had the most dramatic effects on walking speed and percentages of time spent in the single and double support phases of the gait cycle, while the WalkAide had the largest effects on cadence and stride time. Interestingly, the hinged AFO and WalkAide elicited nearly identical improvements in the wearer's step width, step length, stride length, and step and swing times. Based on devices' orthotic effects on mobility parameters, the Ottobock AFO provides the least amount benefit, while the hinged AFO and WalkAide devices had different pros and cons. The hinged AFO created much larger

improvements in walking speed and percentages of time spent in single and double support than the WalkAide, but it surpassed the values of the control group. The FES device allowed the participant to have much faster stride times and much lower cadence than the hinged AFO; meaning that FES allowed her to take longer and fewer steps overall. The effects of the FES device allowed the participant to walk more naturally and brought many of her average parameters the closest to the control group's values as shown in Table 8.1. Therefore, when considering the overall effects of devices on mobility, FES was the most beneficial followed by the hinged AFO and then the Ottobock AFO.

Table 8.1: Mobility Parameter Summary for Case Study

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
AFO-user_01 (Unaided)	0.93 ± 0.16	130 ± 15	0.13 ± 0.03	0.44 ± 0.06	0.87 ± 0.10	0.47 ± 0.05	0.94 ± 0.06	0.63 ± 0.05	0.31 ± 0.02	32.78 ± 1.63	34.35 ± 2.44
AFO-user_01 (Ottobock)	0.97 ± 0.13	128 ± 12	0.12 ± 0.02	0.46 ± 0.05	0.91 ± 0.08	0.47 ± 0.04	0.95 ± 0.05	0.64 ± 0.04	0.31 ± 0.02	32.90 ± 1.63	34.18 ± 1.99
AFO-user_04 (Hinged)	1.14 ± 0.13	128 ± 15	0.10 ± 0.03	0.54 ± 0.06	1.08 ± 0.08	0.48 ± 0.06	0.95 ± 0.05	0.62 ± 0.04	0.32 ± 0.03	34.01 ± 2.35	31.79 ± 2.24
FES-user_01 (WalkAide)	1.07 ± 0.13	122 ± 15	0.09 ± 0.04	0.53 ± 0.05	1.06 ± 0.07	0.50 ± 0.06	1.00 ± 0.06	0.67 ± 0.05	0.33 ± 0.02	33.21 ± 1.53	33.50 ± 1.81
control_group	1.04 ± 0.15	105 ± 10	0.15 ± 0.04	0.60 ± 0.07	1.19 ± 0.14	0.58 ± 0.05	1.15 ± 0.10	0.77 ± 0.08	0.38 ± 0.03	33.14 ± 0.93	33.62 ± 1.82

Table 8.2: Orthotic Effects of Devices on Mobility Parameters for Case Study

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
AFO-user_01 (Ottobock)	+0.04	-2	-0.01	+0.02	+0.04	0.00	+0.01	+0.01	0.00	+0.12	-0.17
AFO-user_04 (Hinged)	+0.21	-2	-0.03	+0.10	+0.21	+0.01	+0.01	-0.01	+0.01	+1.23	-2.56
FES-user_01 (WalkAide)	+0.14	-7	-0.04	+0.09	+0.19	+0.03	+0.06	+0.04	+0.02	+0.43	-0.85

Table 8.3 provides the degree of asymmetry for each device trial, where negative signs indicate that the value of the right leg was greater than the left. To aid comparisons, Table 8.4 provides the orthotic effects of devices on degree of asymmetry, where negative signs indicate devices decreased the degree of asymmetry compared to the baseline trial. The values in Table 8.4 were calculated as the absolute value of the aided trial minus the absolute value of the unaided trial. Unexpectedly, all three devices worsened the wearer's degree of asymmetry except for two instances where the Ottobock actually decreased asymmetry by 2% for step time and 1% for step length. As shown in Table 8.3, the Ottobock made the wearer's step time asymmetry match the control group's average; and across all seven parameters evaluated for symmetry, the Ottobock produced the smallest degree of asymmetry when compared to the hinged AFO and WalkAide. The Ottobock's asymmetry values were only 1% lower than the WalkAide for stance time and percentages of time spent in the stance, swing, and single support phases of the gait cycle. In addition, the Ottobock's degree of asymmetry matched the WalkAide for swing time and matched

the hinged AFO for stance time. Therefore, although the Ottobock provided improvements in symmetry for step length and step time, it did not greatly outperform the hinged AFO or WalkAide in the other five parameters. Comparing the hinged AFO to the Ottobock and WalkAide reveals that the hinged AFO caused the worst asymmetry in step length, swing time, and percentages of time spent in swing and single support. The hinged AFO only caused 1% less asymmetry than the WalkAide for step time, but both values were quite high. In summary, the Ottobock AFO generated the lowest amount of asymmetry while the hinged AFO caused the worst because it had the highest degrees of asymmetry for five out of the seven evaluated parameters.

As seen in Table 7.12, all three devices produced negligible changes in the case study participant's RPE and walking confidence, except for a moderate improvement in RPE with the hinged AFO. Therefore, although devices provided quantifiable, and clinically relevant gait changes within the multimodal environment, their use did not significantly influence perceived amounts walking effort or confidence. Lastly, this study's OMs were compared to the evidence statements provided in Chapter 2.6, which were quoted from the author's systematic literature review publication with Prosthetics and Orthotic International in 2022. This study's results support and oppose some of the evidence statements. Regarding evidence statement one, this study corroborates that FES causes clinically significant increases in walking speed. For evidence statement two, this study agrees that FES generates beneficial kinematic changes, but disagrees with its claim that FES's changes are superior to those of AFOs because the WalkAide in this study did not consistently outperform the Ottobock or hinged AFOs. Finally, this study disagrees with the third evidence statement's claim that FES causes higher reductions in RPE than AFOs because only the hinged AFO in this study caused a notable decrease in RPE.

Table 8.3: Degree of Asymmetry for Case Study

Participant	Step Length (m)	Step Time (s)	Stance Time (s)	Swing Time (s)	Stance %	Swing %	Single Support %
AFO-user_01 (Unaided)	5%	-17%	0%	-3%	1%	-3%	5%
AFO-user_01 (Ottobock)	4%	-15%	2%	-6%	2%	-5%	6%
AFO-user_04 (Hinged)	15%	-19%	2%	-9%	4%	-8%	11%
FES-user_01 (WalkAide)	9%	-20%	3%	-6%	3%	-6%	7%
control_group	4% ± 2%	2% ± 1%	1% ± 1%	2% ± 2%	1% ± 1%	2% ± 1%	2% ± 1%

Table 8.4: Orthotic Effects of Devices on Degree of Asymmetry for Case Study

Participant	Step Length (m)	Step Time (s)	Stance Time (s)	Swing Time (s)	Stance %	Swing %	Single Support %
AFO-user_01 (Ottobock)	-1%	-2%	2%	3%	1%	2%	1%
AFO-user_04 (Hinged)	10%	2%	2%	6%	3%	5%	6%
FES-user_01 (WalkAide)	4%	3%	3%	3%	2%	3%	2%

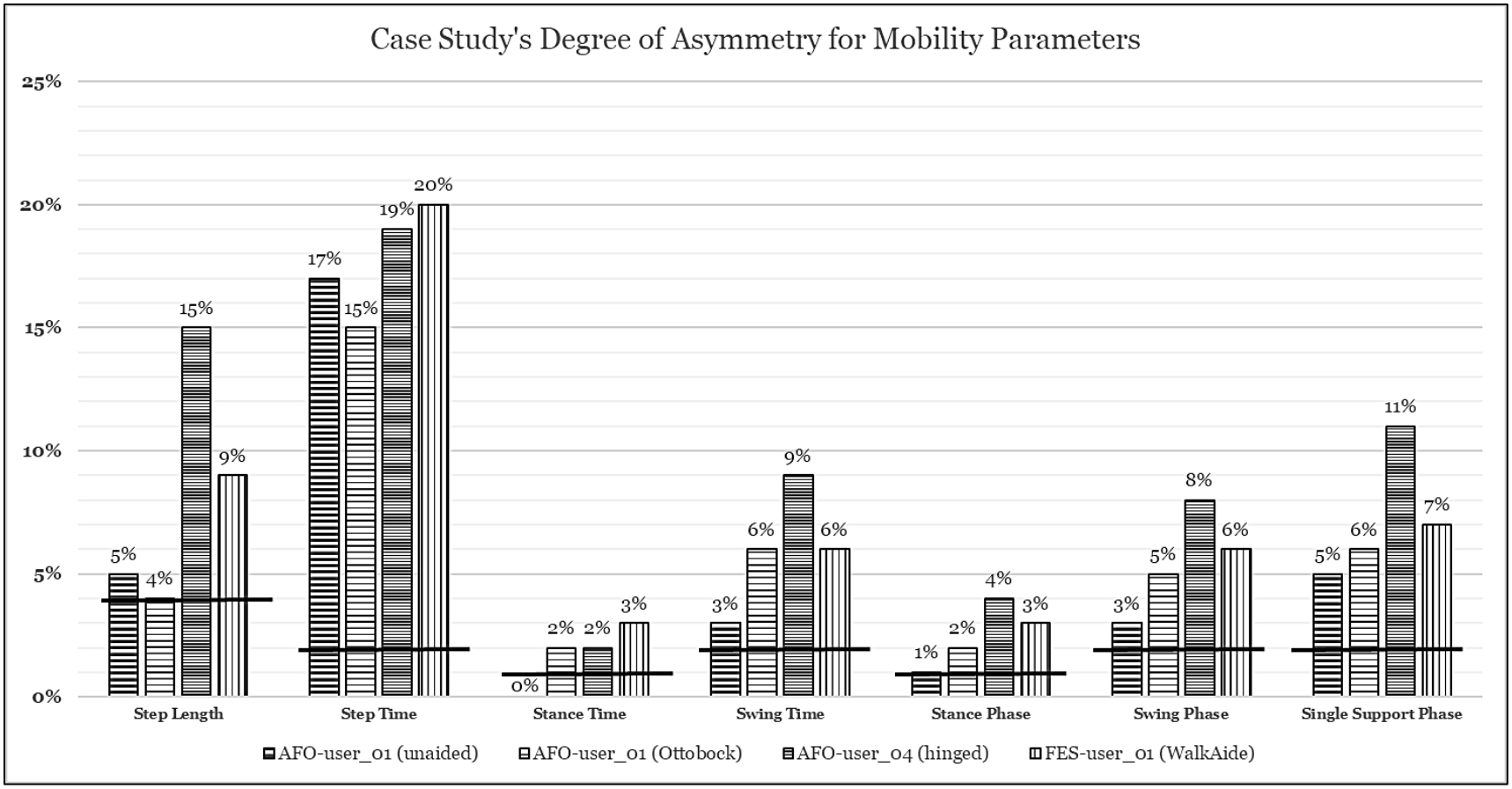

Figure 8.7: Case Study's Degree of Asymmetry with Control Group's Average as Threshold Bar

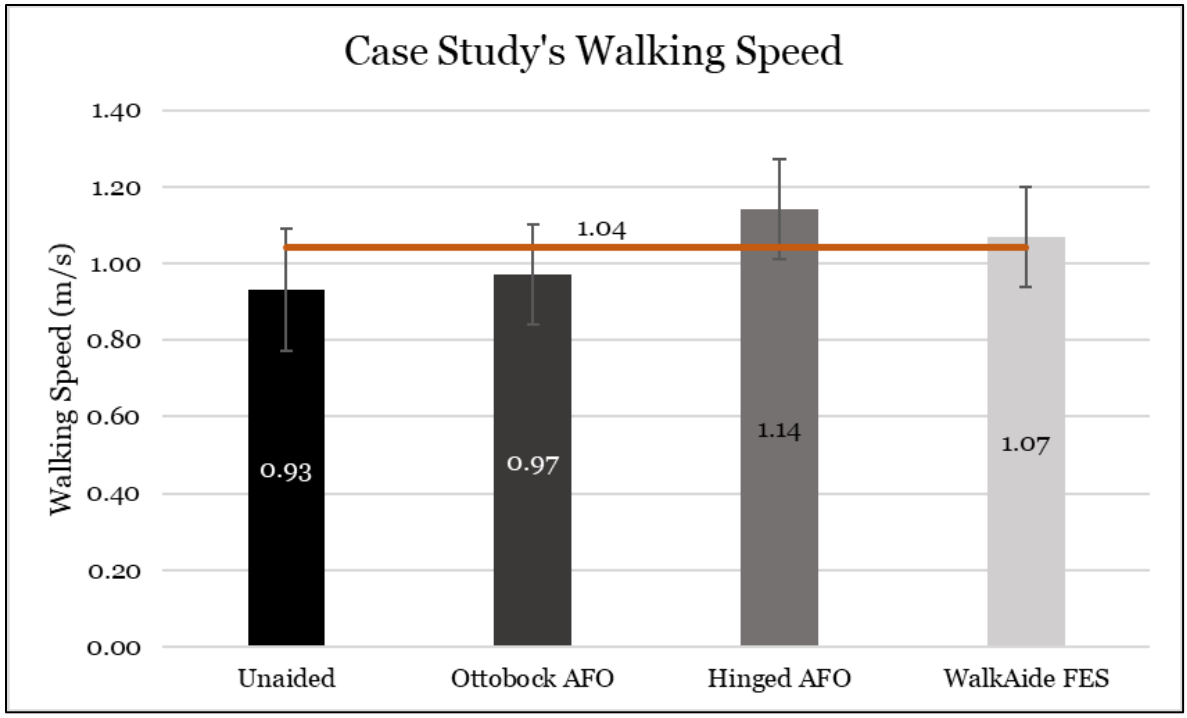

Figure 8.8: Walking Speed for Case Study's Trials with Control Group's Average as Threshold Bar

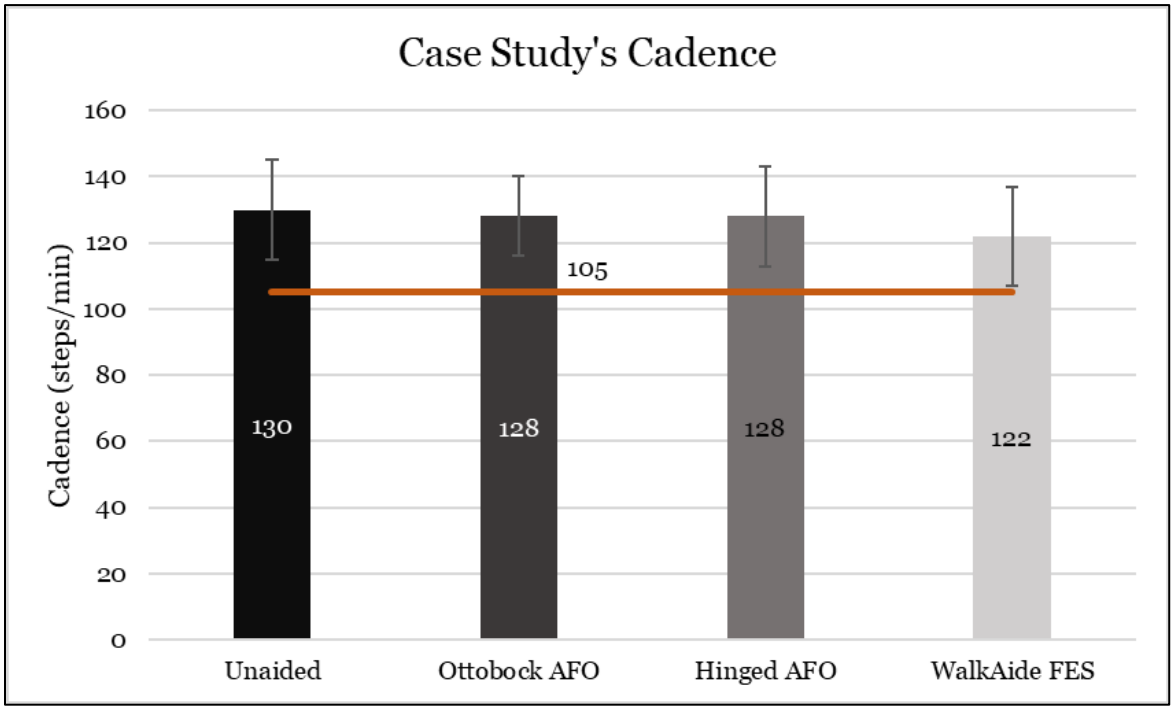

Figure 8.9: Cadence for Case Study's Trials with Control Group's Average as Threshold Bar

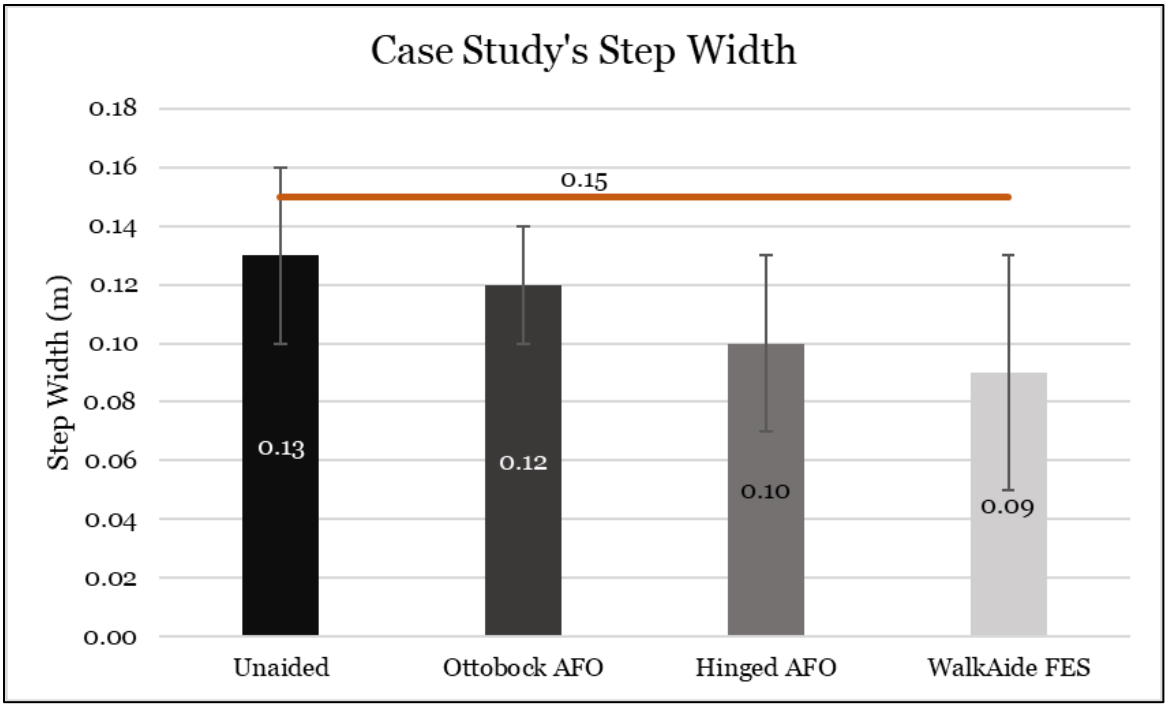

Figure 8.10: Step Width for Case Study's Trials with Control Group's Average as Threshold Bar

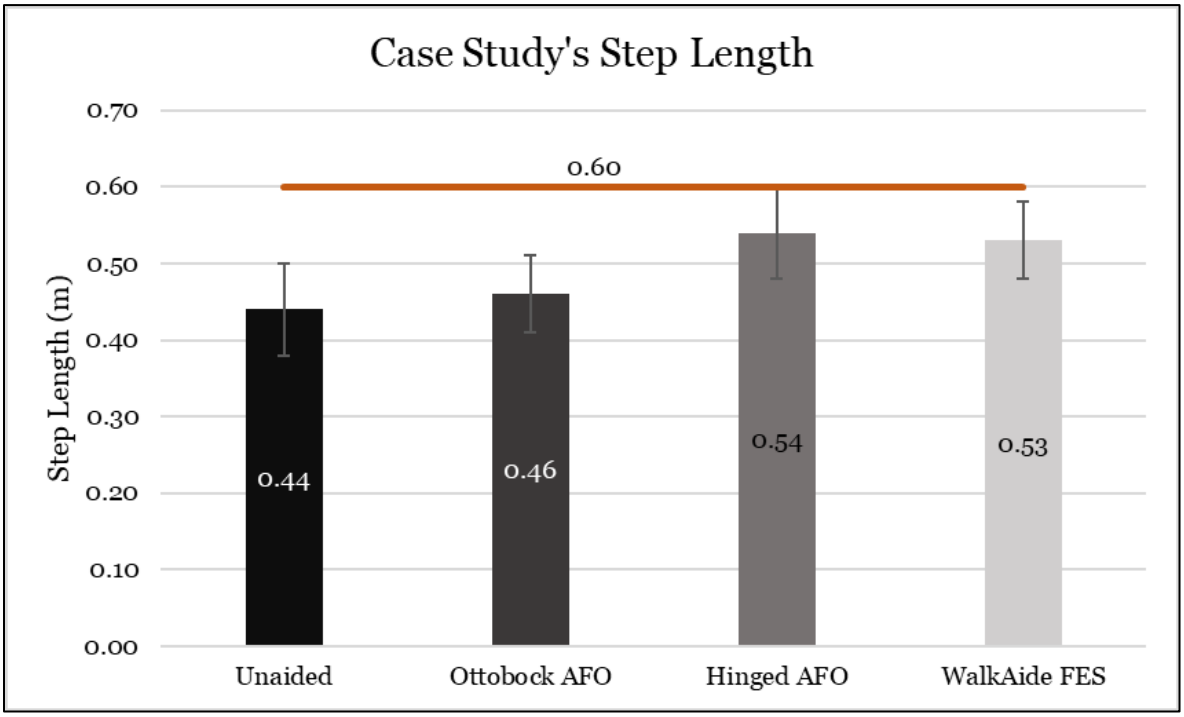

Figure 8.11: Step Length for Case Study's Trials with Control Group's Average as Threshold Bar

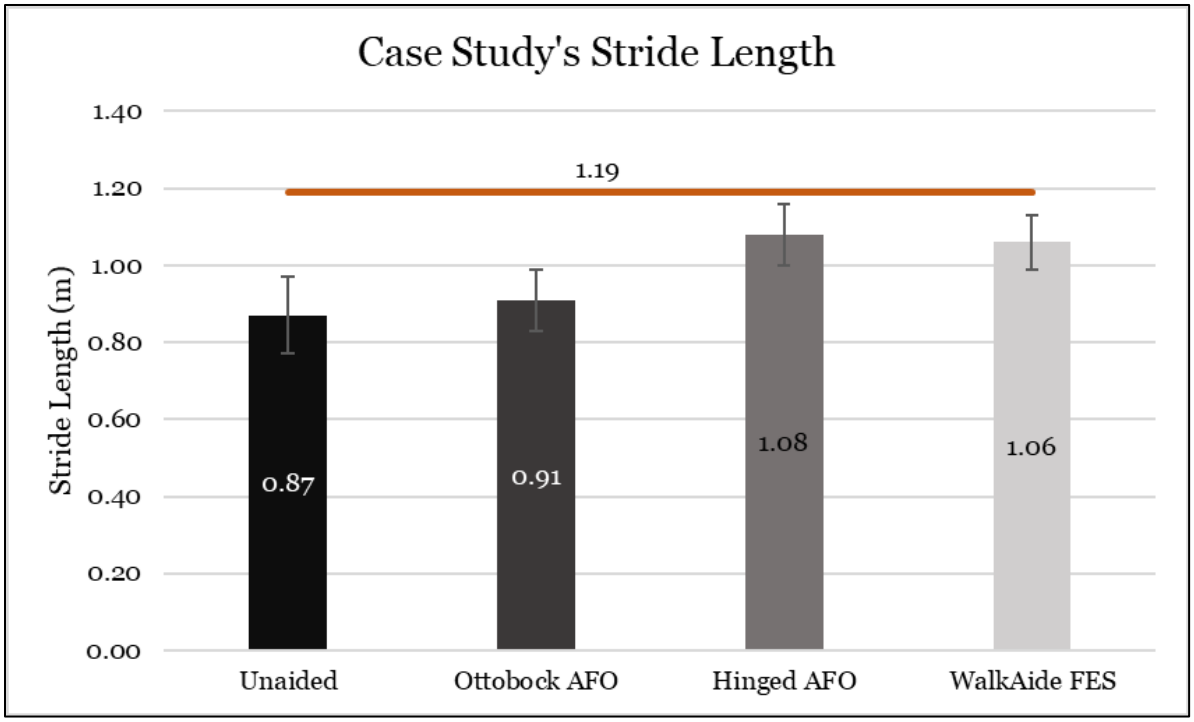

Figure 8.12: Stride Length for Case Study's Trials with Control Group's Average as Threshold Bar

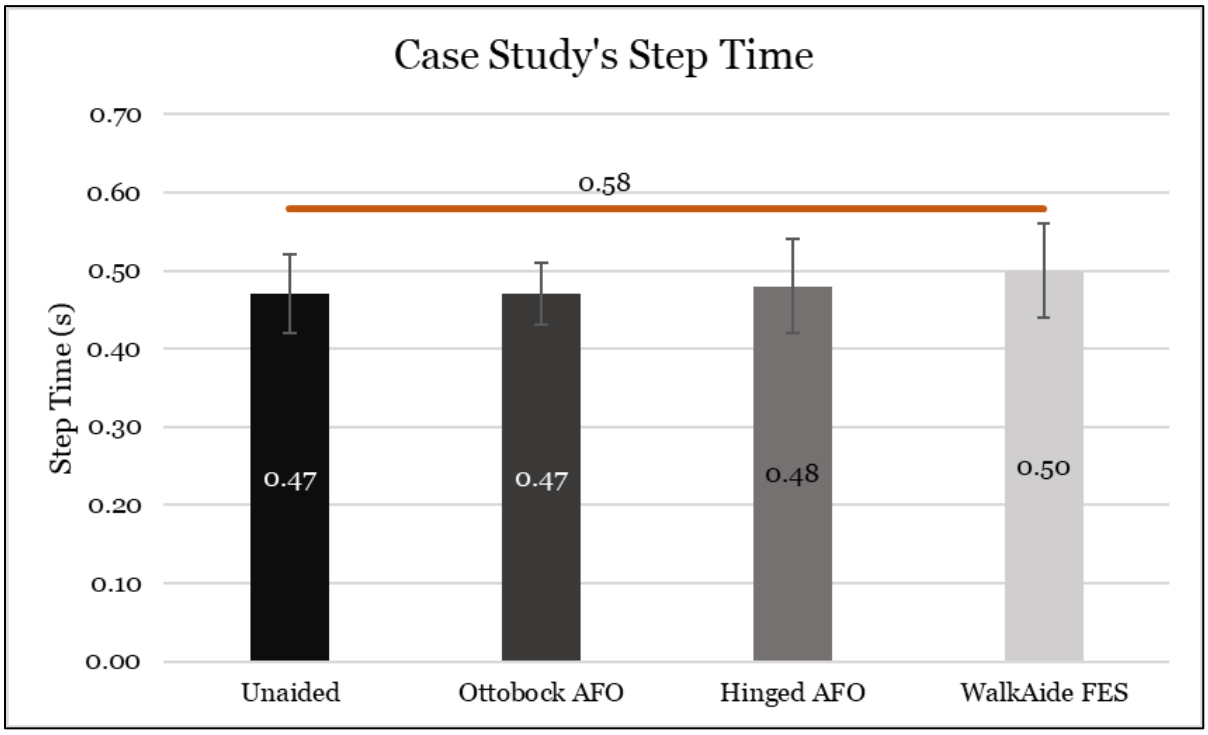

Figure 8.13: Step Time for Case Study's Trials with Control Group's Average as Threshold Bar

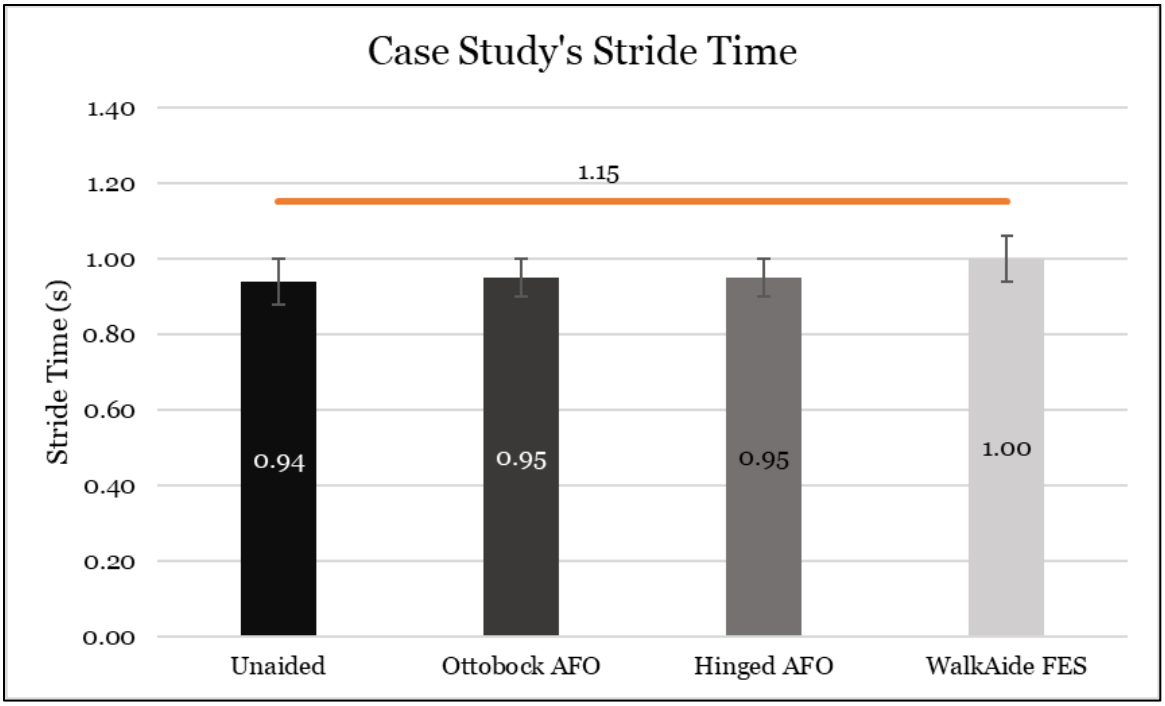

Figure 8.14: Stride Time for Case Study's Trials with Control Group's Average as Threshold Bar

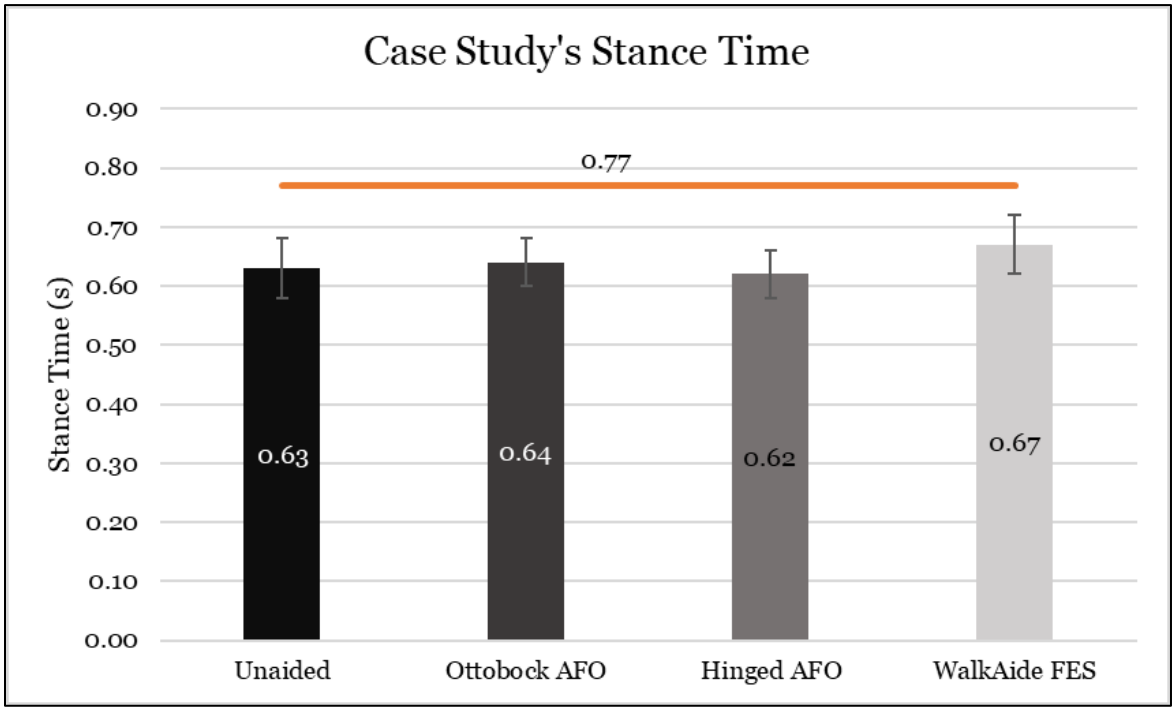

Figure 8.15: Stance Time for Case Study's Trials with Control Group's Average as Threshold Bar

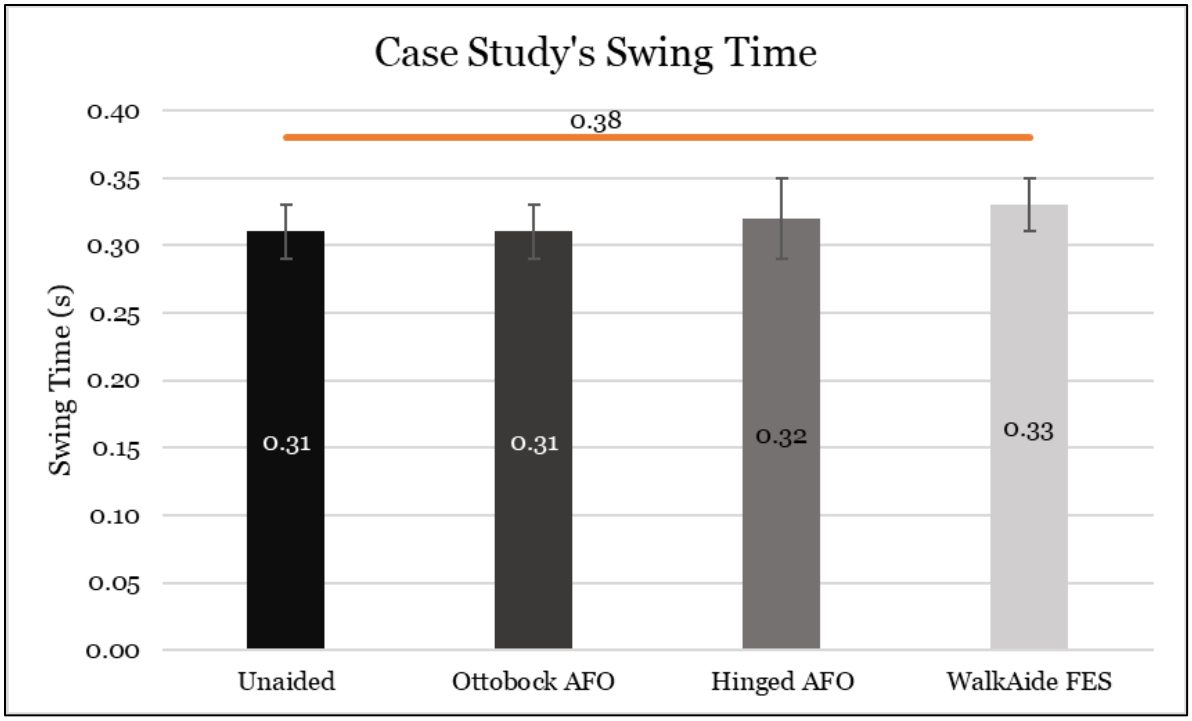

Figure 8.16: Swing Time for Case Study's Trials with Control Group's Average as Threshold Bar

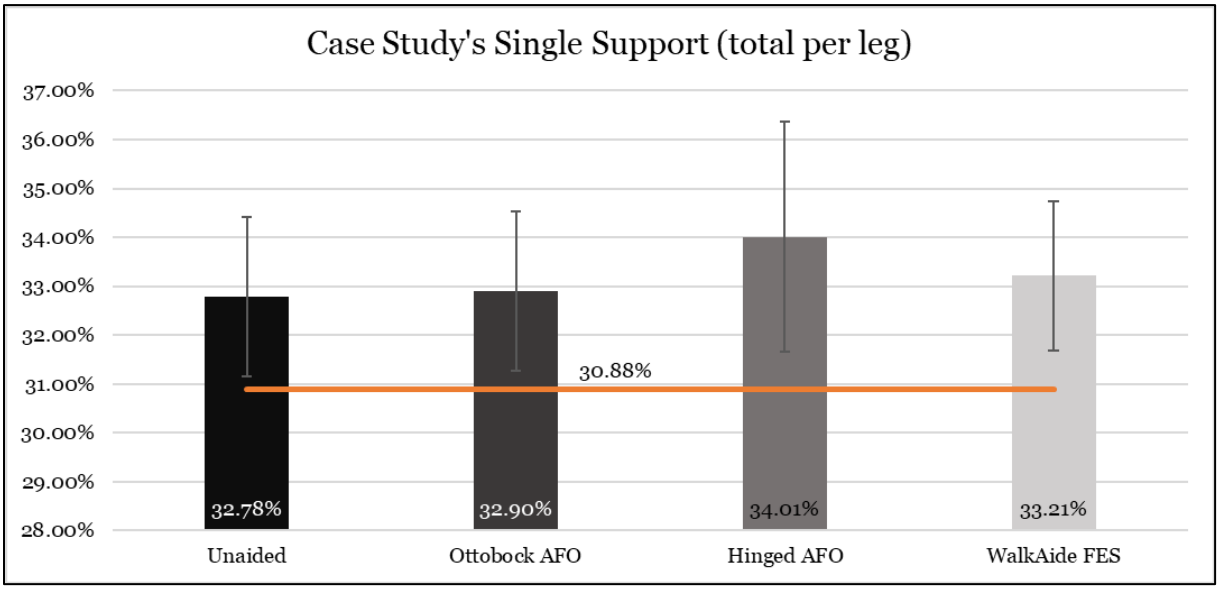

Figure 8.17: Single Support Percentage for Case Study's Trials with Control Group's Average as Threshold Bar

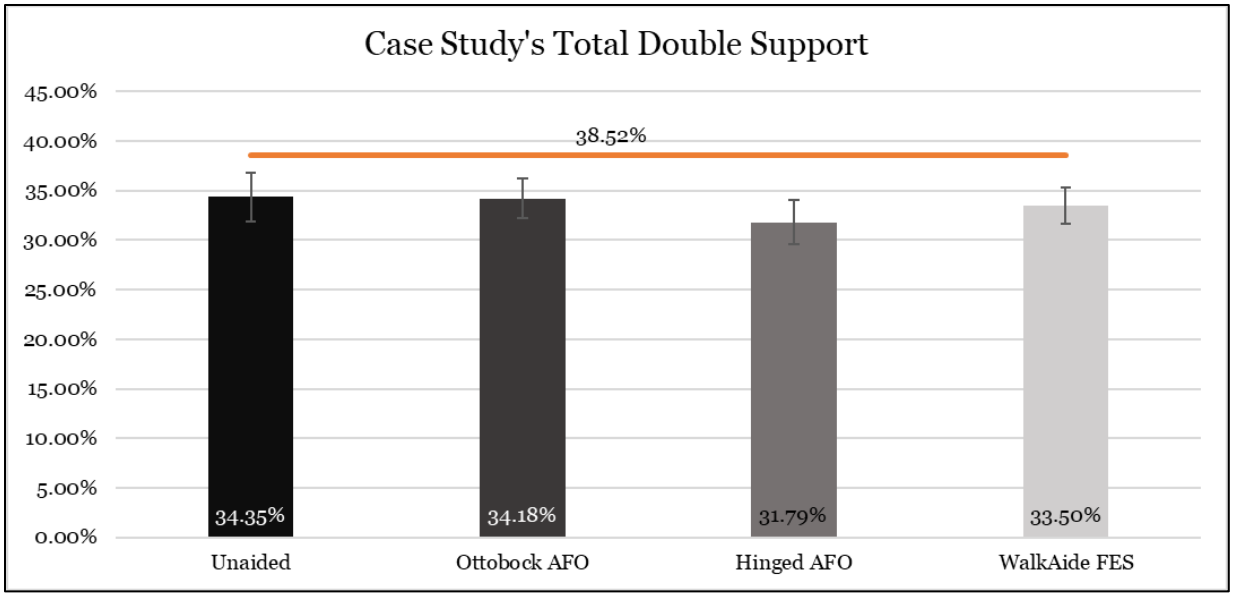

Figure 8.18: Double Support Percentage for Case Study's Trials with Control Group's Average as Threshold Bar

Chapter 9: Conclusions, Contributions, Limitations, and Future Work

pwMS are routinely prescribed AFO and FES devices to address foot-drop, but most gait studies have only evaluated their effects within highly controlled and idealized clinical environments. The environments encountered in everyday life are complex and demanding; they often contain changes in floor pitch and audiovisual stimuli, and people typically perform multiple tasks while they walk. Realistic walking environments are multimodal in nature and can be challenging for pwMS to navigate. This dissertation explored how walking within a multimodal environment affects gait in pwMS who use AFO and FES devices. To accomplish this, the author used a CAREN system to create a novel testing environment. The customized program presented participants with a challenging, yet achievable, scenario: a realistic nature pathway containing multiple changes in floor pitch, audiovisual stimulation, and dual-tasking. This multimodal system gave participants complete, passive control of their walking speeds so they could walk as naturally as possible. A full-body motion capture marker set and force plates were used to collect quantitative data while questionnaires were used to collect qualitative data.

9.1 Conclusions

This study analyzed a normative cohort of thirteen participants aged 28 to 64 years; a cohort of three AFO-users aged 58 to 63 years, which included both of the case study's AFO trials; and a case study of a pwMS, 58 years of age, who used two types of AFOs and an FES device. The sessions completed by pwMS resulted in five aided trials that allowed the orthotic effects of three different foot-drop devices to be analyzed: the

Ottobock carbon fiber Walk-On Flex AFO, a plastic hinged AFO, and the WalkAide FES. This study's primary outcome measures are quantitative and related to overall mobility, gait symmetry, and orthotic gait. Secondary outcome measures are qualitative and were gathered through Likert questionnaires: ratings of perceived exertion and confidence in walking ability. The evaluated mobility parameters are walking speed, step width, step length, step time, stride time, stance time, swing time, cadence, and percentage of time spent in the single and double support phases of ambulation. The gait symmetry parameters are stance time, swing time, step length, step time, and percentage of time spent in the stance, swing, and single support phases of ambulation. Orthotic gait was evaluated for each mobility and symmetry parameter listed above for all pwMS.

Aside from providing a normative data set for comparisons, the control group's results validated both this study's protocols and the multimodal environment. For controls, multimodal walking produced two notable gait effects: (1) participants exhibited the largest variabilities in their step width and walking speed, and (2) participants spent more time in the stance phase of the gait cycle when compared to normative values that used flat ground. Controls were comfortable on CAREN and felt confident in their walking capabilities and perceived their required level of exertion as being very light. Both for controls and all pwMS, participant demographics did not impact the patterns seen in walking performance or significantly alter perceptions of walking confidence or exertion.

AFOs produced mixed effects for pwMS but were predominantly beneficial. AFOs improved most of the mobility parameters enough for them to match or become competitive with those of the control group, but some parameters were worsened when compared to unaided trials which increased their disparity with controls. AFOs improved gait symmetry parameters with few exceptions, but their values were still much higher

than controls – other than stance time and stance percentage which were only 3% higher. With few exceptions, AFOs also lowered the standard deviations (variability) within all mobility and symmetry parameters; they even brought the variability of some group parameters within 1% of those exhibited by controls. Even though AFO devices created quantitative and clinically relevant improvements in overall ambulation, pwMS did not believe they improved walking confidence or RPE. Although pwMS ranked perceived exertion much higher than controls, their walking confidence scores were comparable.

The case study participant experienced mixed effects from her devices. Comparing the mobility parameter effects of devices against each other and the control group reveals that the Ottobock provided the least overall benefit while the WalkAide produced the most parameters with values close to those of controls. The hinged AFO's overall benefits on mobility were somewhere between the other devices even though it produced the fastest walking speed. All three devices improved gait consistency by decreasing the variability within mobility and symmetry parameters. All three devices worsened degree of asymmetry except for two instances where the Ottobock slightly improved symmetry for step length and step time. When considering overall gait symmetry, the Ottobock generated the lowest amount of asymmetry across all seven evaluated parameters while the hinged AFO created the highest degrees of asymmetry for five out of the seven parameters. Lastly, although devices provided quantifiable, and clinically relevant gait changes within the multimodal environment, their use did not significantly influence perceived amounts of walking effort or confidence. From a clinical standpoint, the results of the case study suggest that device prescriptions can be fine-tuned to address symmetry or overall mobility depending on the individual's physical needs or desired activities. For instance, a pwMS who exhibits high levels of asymmetry from foot-drop may benefit more

from using an Ottobock than a hinged AFO or FES, whereas someone with fairly symmetric gait who wants to move around faster may benefit more from using FES or a hinged AFO rather than an Ottobock. More evidence is required to confirm this; and overall, more studies need to be conducted with multimodal environments to further explore the impacts of realistic walking conditions on gait.

9.2 Contributions to Literature

This dissertation provides a unique experimental setup that was customized to be responsive, safe, and challenging yet achievable for pwMS with foot-drop to navigate both with and without the use of an orthotic device. The setup and protocols were well tolerated by all participants with MS. Because foot-drop device effects on and perceptions of pwMS while ambulating within environments similar to those encountered in everyday life are not well understood, this dissertation provides several contributions to the literature:

- A customized CAREN program that:
  - produces a realistic, multimodal walking environment containing changes in pitch, audiovisual distractions, and during trial tasks for dual-tasking.
  - utilizes a self-paced mode that gives participants complete, passive control of the treadmill's speed – allowing them to ambulate as naturally as possible.
  - operates with Motek's 2020, 46-count full-body motion capture marker set.
  - collects continuous full-body motion capture and force plate data.
  - runs Motek's HBM software in real-time and records .mox files that can be post-processed within Motek's GOAT software.
  - is well tolerated by pwMS exhibiting unilateral foot-drop with PDDS of level 5.
- A robust study design and protocol that can be easily replicated for future studies and modified to evaluate other populations, gait impediments, or devices.

- A case study of a 58-year-old pwMS with a PDDS of 4 who completed trials with three different devices: Ottobock's carbon fiber Walk-On Flex AFO, a custom formed hinged AFO made of plastic, and WalkAide's FES. Four walking trial conditions were gathered and used for analysis – three different device trials and one trial without a device to provide a baseline. Analysis includes the following:
    - eleven mobility parameters which were compared across all four trial types and against the control group's averages.
    - seven spatiotemporal parameters which were evaluated for symmetry and compared to those of the control group.
    - orthotic effects of each device for all mobility and symmetry parameters.
    - perceptions of exertion and walking confidence for each trial case which were compared to the control group's averages.
- Analysis of a cohort of three AFO-users aged 58 to 63 years with PDDS scores of 4 and 5. This cohort includes the case study's two AFO trials. Altogether, the AFO group consists of four different device trials: three using Ottobock's carbon fiber Walk-On Flex and one with the custom formed hinged AFO. Analysis performed on the AFO group included all those listed under the case study above.
- Analysis of a normative cohort of thirteen participants aged 28 to 64 years to validate the experimental setup and provide reference data to compare pwMS against. Analysis included eleven mobility parameters, seven symmetry parameters, and RPE and walking confidence scores.
- Lastly, a variety of observations made by the PI and participant feedback regarding device usage and the experimental setup where documented and provided.

9.3 Limitations and Future Work

The main limitation of this study was the sample size of pwMS. There were only three participants with MS, and they were all female with similar PDDS. Providing monetary incentives, supplying the foot-drop devices, or having access to a registry or database that can locate appropriate participants would greatly assist with recruitment. A larger group of pwMS is necessary to determine substantiated statistical significance; and more varied participant demographics is required to investigate if device effects have a connection to gender, level of disability, type of MS, medication usage, etc. Although gathering information about physical activities was useful, it did not necessarily reflect fitness levels. Collecting quantifiable biometric data such as heart rate, Vo2 max, and body temperature during multimodal walking could allow interesting and clinically relevant evaluations. Exploring how a multimodal environment influences participant frustration levels and employed movements while trying to hit targets could also be quite interesting.

This study's protocols were focused on analyzing overall gait parameters during aided and unaided ambulation within a multimodal environment with several stimuli active all at once, so the ability to discretely analyze the effects of each element of the multimodal environment was limited. Because multitasking was incorporated throughout the entirety of the walking trials, it was not possible to isolate large enough sections to investigate the effects of walking with and without multitasking. Exploring the effects of zero-degree versus sloped pitch within the multimodal environment was inhibited by the number of valid gait cycles that could be parsed for analysis. However, this dissertation was able to parse a minimum of seven left and right cycles for gait analysis during flat ground walking. The mobility parameter comparisons between the flat ground segment of each trial for pwMS versus their overall multimodal trials is provided in section 7.2.2.5.

The results of these comparisons suggest that there may be clinically relevant trends between flat and sloped multimodal ambulation. For instance, the differences between the flat ground segments and complete multimodal trials suggest participants with MS typically felt more unstable during the flat, beginning segment than during their overall multimodal trials – which held true for both unaided and aided trials. Most participants had a combination of larger step widths and shorter step and stride lengths during the flat segment than during their full multimodal trials. Perhaps this was due to them getting familiar with CAREN's self-paced mode or having more energy and excitement earlier during each trial; or perhaps the smaller number of gait cycles analyzed for the flat segments skewed the values. A future study could explore this topic more systematically by gathering discrete trials, using identical simulations and total walking distances, with the following pitch conditions: zero pitch, set incline, and set decline. This study demonstrated that pwMS with PDDS scores of 4 and 5 could safely navigate pitch settings of ±2˚, but a future study that explores multiple pitch settings systematically may also produce interesting insights. Lastly, completing all the aforementioned trial types with and without the multitasking element could provide even more insights into how the different elements of a multimodal environment affect gait and perceptions.

Because this dissertation was designed for a larger cohort of pwMS, a follow-up study could easily use it as a foundation. It can be modified to investigate other populations, gait impediments, or devices. Additionally, the raw data collected during this study could be used as part of a meta-analysis or used as-is to investigate other outcome measures. Device effects on engrained compensatory motions (such as hip hiking, circular hip abduction, and high stepping) should analyze hip adduction/abduction, knee flexion/extension, and ground clearance between unaided and aided multimodal trials.

Understanding how devices affect posture and stability during ambulation would be achieved by analyzing margins of stability, torso alignment, and head range of motion. Examining head range of motion, eye movements, and lateral drifting while ambulating could also provide insights on levels of disorientation and loss of proprioception while walking and multitasking. Although this study contains the raw data required to address many of the aforementioned parameters, they were outside of this study's original scope. Grouping these parameters as described above would produce well-rounded and focused analyses that could be published separately from those contained in this dissertation.

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Appendix A: Copyright Permissions

The introductory section of Chapter 1 (pages 3-5) and section 2.6 of Chapter 2 (pages 33-35) of this dissertation have been previously published in Prosthetics and Orthotics International in 2022. Content has been reproduced with permission from Wolters Kluwer and the article is cited within the text. The reproduced portions are largely paraphrased, expanded upon, and tailored for use within this dissertation. The original publication contains information and insights beyond those cited in this dissertation.

For the PDDS scale used in this dissertation and provided in Appendix E, copyright permissions are not required, but the following acknowledges and cites the authors associated with NARCOMS who originally developed it.

Patient Determined Disease Steps (PDDS)

The Patient Determined Disease Steps (PDDS) is a self-assessment scale of multiple sclerosis disease status collected in the North American Research Consortium on Multiple Sclerosis (NARCOMS) Registry at enrollment and semi-annual follow up surveys. The PDDS is not a copyrighted instrument, however the authors of PDDS request that if you use the PDDS as given below or from www.NARCOMS.org/PDDS that NARCOMS be acknowledged when using or publishing work with these questions and that the following references be cited:

PDDS:

Hohol MJ, Orav EJ, Weiner HL. Disease Steps in multiple sclerosis: A simple approach to evaluate disease progression. Neurology 1995; 45: 251–55.

Hohol MJ, Orav EJ, Weiner HL. Disease Steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. Multiple Sclerosis 1999; 5: 349–54.

Marrie RA and Goldman M. Validity of performance scales for disability assessment in multiple sclerosis. Multiple Sclerosis 2007; 13: 1176-1182.

Acknowledgement for use:

The PDDS is provided for use by the NARCOMS Registry: www.narcoms.org/pdds. NARCOMS is supported in part by the Consortium of Multiple Sclerosis Centers (CMSC) and the CMSC Foundation.

We hope the PDDS is useful in your studies, and appreciate the above citations and references.

[redacted]

Robert Fox, MD
Managing Director
NARCOMS

[redacted]

Ruth Ann Marrie, MD, PhD
Scientific Director
NARCOMS

Appendix B: Institutional Review Board Information

The author acquired Institutional Review Board approval to conduct this study and was assigned with Pro#00040564. The following pages contain screenshots of the informed consent documentation exactly as approved by the review board and provided to participants, but with principal investigator's email and phone number redacted.

USF
UNIVERSITY OF SOUTH FLORIDA

Informed Consent to Participate in Research

Information to Consider Before Taking Part in this Research Study

Title: A Comparative Study of Foot-drop Treatments on pwMS using a Realistic Walking Environment

Pro # 00040564

Overview: You are being asked to take part in a research study. The information in this document should help you to decide if you would like to participate. The sections in this Overview provide the basic information about the study. More detailed information is provided in the remainder of the document.

Study Staff: This study is being led by Laura Byrnes-Blanco who is a Study Coordinator and Doctoral Candidate at the University of South Florida (USF). She is called the Principal Investigator. She is being guided in this research by Stephanie Carey, Rajiv Dubey, and Derrick Robertson. Other approved research staff may act on behalf of the Principal Investigator.

Study Details: This study is being conducted at the USF College of Engineering. Its purpose is to compare the effects of ankle-foot-orthosis (AFO) and functional electrical stimulation (FES) devices on persons with multiple sclerosis. More specifically, it aims to compare device effects when the wearer is walking in a realistic environment. AFOs are limited to rigid plastic boot styles and FES is limited to the WalkAide or Bioness L300. You only need to complete **one data collection session.** You will be **required** to wear a full-body motion capture marker-set and upper body safety harness while walking on the virtual reality system. If you have multiple sclerosis, your data collection session is estimated to take **2 hours**. If you do not have multiple sclerosis, your data collection session is estimated to take **1.5 hours.** If you have foot-drop, you are required to bring and use your personal AFO or FES device as previously requested. If you use a foot-drop device, you will be asked to complete two walking trials: one with and one without your device. If you do not use a foot-drop device, you will be asked to complete one unaided walking trial. All walking trials will be done on a virtual reality system containing a treadmill and motion platform.

Participants: You are being asked to take part in this study because you (1) have multiple sclerosis *and* consistently use an AFO or WalkAide or Bioness L300 device to treat unilateral foot-drop **or** (2) have no walking limitations. We want to determine AFO and WalkAide/Bioness L300 effectiveness at correcting foot-drop while wearers walk in a realistic environment. This realistic environment contains changes in elevation (floor slope), during-trial tasks, visual displays, and sounds.

Voluntary Participation: Your participation is voluntary. You do not have to participate and may stop your participation at any time. There will be no penalties or loss of benefits or opportunities if you do not participate or decide to stop once you start.

Benefits, Compensation, and Risk: We do not know if you will receive any benefit from your participation. There is no cost to participate except for travel costs to/from USF. You will not be compensated for your participation, but will receive a free parking pass. This research is considered **minimal risk**. Minimal risk means that study risks are the same as the risks you face in daily life. The most common and most serious risks that may be related to taking part in this research include fatigue, trips, and falls. But remember that a safety harness will be used to prevent complete falls.

Confidentiality: If we publish this study's findings, we will keep your study information private and confidential. Anyone with the authority to look at your records must keep them confidential.

Why are you being asked to take part?

You are being asked to take part in this study because you (1) have multiple sclerosis and consistently use an AFO or WalkAide or Bioness L300 device to treat unilateral foot-drop **or** (2) have no walking limitations. You also satisfy the eligibility criteria.

Study Procedures: What will happen during this study?

The effectiveness of AFO and FES foot-drop devices on persons with multiple sclerosis within realistic walking environments is unknown. To explore this topic, we are using a top-of-the-line rehabilitation system called CAREN (Computer Assisted Rehabilitation ENvironment). CAREN will provide you with a realistic environment in which you can walk normally and interact with virtual objects. CAREN can adapt to your walking speed in real time. Therefore, you will walk at a self-selected pace. You will be asked to hit virtual targets while walking on CAREN. If you use a foot-drop device, you will be asked to use your *personal* device for one trial; and asked to do another trial without using any device. **Only you will operate your device. You will be asked to operate your device as usual. No alterations to devices or their usage will occur.** If you do not use a foot-drop device, you will be asked to complete one walking trial without using any devices. **No drugs or experimental devices will be used in this study.**

You only need to attend one data collection session. This session will last 1.5 hours if you do not have multiple sclerosis. This session will last 2 hours if you do have multiple sclerosis. Your walking trial will be completed on CAREN while you wear an upper body safety harness and full-body motion capture marker-set. These markers are small and will be placed on you body in the following locations with special double-sided tape: C7 and T10 vertebra, xiphoid process, jugular notch, front and back pelvic iliac spines, left and right thighs and calves, left and right knees, left and right elbows, left and right ankles and feet, left and right shoulders, left and right wrists and hands, and a headband for head markers.

CAREN will display a virtual outdoor environment for you to walk in. CAREN's visual displays will match the movements of the treadmill platform. CAREN will present visual distractions and targets for you to hit while you walk. It will also use surround sound speakers to provide ambient noises and distractive sounds. You will have a rest period between all walking trials. You will be asked to answer 2 short questionnaires about your walking experience after each trial. On the next page, there is a table that summarizes what will happen during your data collection session after you have signed this consent form.

Table 1: Requirements for Data Collection Sessions

You will be asked to:	Reason
Wear: (1) your foot-drop device, (2) closed toe shoes, (3) tight fitting clothing (preferably athletic attire without reflective markings), and (4) long hair in a ponytail or bun	Necessary for proper data collection and participant safety
Fill out the "Basic Subject Data" sheet	Necessary for data analysis, participant safety and data validity
Have 46 reflective markers placed on your body's joints and prominent features via double-side tape and a headband	Required for CAREN operation and data collection
Be escorted on/off CAREN and secured to it with an upper-body safety harness by a member of the research team	Participant safety
Perform basic motions as directed by the research team	System calibration
Walk at a normal pace during walking trials on CAREN	Walking trial and data collection
Complete 2 questionnaires after each walking trial: Borg 6-20 Ratings of Perceived Exertion and 7-point Likert scale for confidence in walking ability	Data collection
Allow us to record walking trials and take a photo of your foot-drop device (only accessible to research team, will not contain identifiable information, and potentially stored for 3 years in secured location before deletion)	Data collection and analysis *(Not mandatory)*

Total Number of Participants

An estimated total of 30 individuals will take part in this study at USF.

Alternatives / Voluntary Participation / Withdrawal

You do not have to participate in this research study.

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study. You are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study.

You can decide after signing this informed consent document that you no longer want to take part in this study for any reason at any time. If you decide you want to stop taking part in the study, tell the study staff as soon as you can.

Please note, even if you want to stay in the study, there may be reasons we will need to withdraw you from the study. You may be taken out of this study if we find out it is not safe for you to stay in the study or if you are not coming for the study visits when scheduled. We will let you know the reason for withdrawing you from this study.

Benefits

We are unsure if you will receive any benefits by taking part in this research study.

Risks or Discomfort

This research is considered **minimal risk**. That means that the risks associated with this study are the same as what you face every day. The following are the specific risks associated with this study:

1. **Fatigue:**
   This study analyzes gait and requires some degree of mental concentration. You may feel a little tired after completing your session.
2. **Trips and Falls:**
   Trips and falls may occur while walking on CAREN, but an upper body safety harness will always be worn. The harness will prevent you from fully falling down.
3. **Skin irritation from motion capture tape or paper tape:**
   The double-sided tape used for the markers is gentler than band-aides. Paper tape is extremely gentle and often used over stitched wounds to keep them sealed. Regardless, these are still sticky and can tug at the skin when removed or cause irritation to sensitive skin.

Compensation

You will receive no payment or other compensation for taking part in this study.

Costs

It will not cost you anything to take part in the study except for the travel costs to/from USF. A complementary parking pass will be provided to you upon your arrival for your data collection session.

Conflict of Interest Statement

No conflict of interest exists for this study.

Privacy and Confidentiality

All in-person interviews and data collection sessions will be done in a private setting. We will do our best to keep your records private and confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Certain people may need to see your study records. These individuals include:

- The research team, including the Principal Investigator, study coordinator, and research staff.
- Certain government and university people who need to know more about the study. For example, individuals who provide oversight on this study may need to look at your records. This is done to make sure that we are doing the study in the right way. They also need to make sure that we are protecting your rights and your safety.
- Any agency of the federal, state, or local government that regulates this research. This includes the Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP).
- The USF Institutional Review Board (IRB) and its related staff who have oversight responsibilities for this study, and staff in USF Research Integrity and Compliance.

We may publish what we learn from this study. If we do, we will not include your name. We will not publish anything that would let people know who you are.

If completing an online survey, it is possible, although unlikely, that unauthorized individuals could gain access to your responses. Confidentiality will be maintained to the degree permitted by the technology

used. No guarantees can be made regarding the interception of data sent via the Internet. However, your participation in this online survey involves risks similar to a person's everyday use of the Internet. If you complete and submit an anonymous survey and later request your data be withdrawn, this may or may not be possible as the researcher may be unable to extract anonymous data from the database.

The following information may be used and disclosed to others:

- Your research records
- Your contact information, including your name, and e-mail address

Your personal information collected for this research will be kept as long as it is needed to conduct this research. Once your participation in the research is over, your information will be stored in accordance with applicable policies and regulations. Your permission to use your personal data will not expire unless you withdraw it in writing. You may withdraw or take away your permission to use and disclose your information at any time. You do this by sending written notice to the Principal Investigator at the following address: [redacted]

While we are conducting the research study, we cannot let you see or copy the research information we have about you. After the research is completed, you have a right to see the information about you, as allowed by USF policies.

If you have concerns about the use or storage of your personal information, you have a right to lodge a complaint with the data supervisory authority in your country.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in this study. We will notify you as soon as possible if such information becomes available.

Clinically relevant results may be disclosed to you if they could significantly benefit you or are requested. We may learn things about you from the study activities that could be important to your health or to your treatment. If this happens, this information will be provided to you. Types of research results that may be returned are parameters concerning gait symmetry and active balance. You will be notified via email. The results will not be placed in your medical record. You may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions.

You can get the answers to your questions, concerns, or complaints.

If you have any questions, concerns, or complaints about this study, call Laura Byrnes-Blanco at: [redacted] or email her at [redacted]. If you have questions about your rights, complaints, or issues as a person taking part in this study, call the USF IRB at (813) 974-5638 or contact by email at RSCH-IRB@usf.edu.

By signing this form, you are giving your permission to use and/or share your health information as described in this document. As part of this research, USF may collect, use, and share the following information:

- Your research record
- Your contact information, including your name, and e-mail address
- Information related to the study's eligibility criteria

You can refuse to sign this form. If you do not sign this form you will not be able to take part in this research study. However, your care outside of this study and benefits will not change. Your authorization to use your health information will not expire unless you revoke (withdraw) it in writing. You can revoke your authorization at any time by sending a letter clearly stating that you wish to withdraw your authorization to use your health information in the research. If you revoke your permission:

- You will no longer be a participant in this research study;
- We will stop collecting new information about you;
- We will use the information collected prior to the revocation of your authorization. This information may already have been used or shared with others, or we may need it to complete and protect the validity of the research; and
- Staff may need to follow-up with you if there is a medical reason to do so.

To revoke your authorization, please write to:

Principal Investigator: Laura Byrnes-Blanco
For IRB Study # 00040564
4202 E. Fowler Avenue, ENG 030,
Tampa, FL 33620, USA

While we are conducting the research study, we cannot let you see or copy the research information we have about you. After the research is completed, you have a right to see the information about you, as allowed by USF policies.

Consent to Take Part in Research

I freely give my consent to take part in this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

Signature of Person Taking Part in Study _____ Date _____

Printed Name of Person Taking Part in Study _____

Consent to Record Video of Walking Trials / Photograph Foot-drop Device

I freely give my consent to have my walking trials recorded / my foot-drop device photographed. I understand that this not mandatory. I understand that I may decline it without altering the rest of my session as agreed upon.

Signature of Person Taking Part in Study _____ Date _____

Printed Name of Person Taking Part in Study _____

Statement of Person Obtaining Informed Consent and Research Authorization

I have carefully explained to the person taking part in the study what he or she can expect from their participation. I confirm that this research participant speaks the language that was used to explain this research and is receiving an informed consent form in their primary language. This research participant has provided legally effective informed consent.

Signature of Person Obtaining Informed Consent _____ Date _____

Printed Name of Person Obtaining Informed Consent _____

Appendix C: Study Application Questionnaire

The following pages contain screen shots of the study application questionnaire. The author created this in Google Forms with her password protected USF Google account. The collected information was used to determine participant eligibility, generate participant demographics, assist with data analysis, and assist with results interpretation.

Eligibility Questionnaire

You must fill out this form to be considered for the study. (All questions are either multiple choice or short answer.) Once your submission is reviewed, you will be notified if you can participate in the study. Your email address is required for results and a copy of your submission to be sent back to you.

* Required

1. Email *

2. I promise to thoroughly read all content and answer questions truthfully and to the best of my knowledge. *

   Mark only one oval.

   - ◯ Yes
   - ◯ No

Informed Consent ** MUST READ **

By submitting this questionnaire, you are agreeing that it may be used for analysis purposes. Only submissions which meet the eligibility criteria will be used for analysis and have all personal identifiers removed from them. This means that your personal information with be kept confidential. Submissions that do not meet the eligibility criteria will be deleted.

Only the Principal Investigator will review questionnaire submissions.

A copy of this questionnaire and your responses will be emailed to you immediately after submission.

THIS STUDY IS COMPLETELY VOLUNTARY. You may stop participating at any time without any consequences. Just notify the Principal Investigator if you choose to stop participating.

3. I have read and understand the terms of submitting this questionnaire. I understand that by submitting this form I am agreeing to take part in research. *

   If you do not give your consent, please exit this questionnaire now and let the Principal Investigator know that you no longer wish to continue.

   Mark only one oval.

   - ◯ I freely give my consent to take part in this research as stated above.

Question Section #1

A few basic questions about you.

4. I have clinically diagnosed multiple sclerosis. *

'Clinically diagnosed' meaning that a neurologist has diagnosed you.

Mark only one oval.

- ◯ Yes
- ◯ No

5. What type of multiple sclerosis do you have? *

Mark only one oval.

- ◯ Relapsing remitting
- ◯ Primary progressive
- ◯ Secondary progressive
- ◯ Progressive relapsing
- ◯ I am not sure what type I have.
- ◯ I do NOT have multiple sclerosis.

6. I experience foot-drop on my: *

('Foot-drop' is difficulty in lifting your toes/foot upwards, which may interfere with your ability to walk heel-to-toe.)

Mark only one oval.

- ◯ Right foot
- ◯ Left foot
- ◯ Both feet
- ◯ I do NOT have foot-drop.

7. Sex (from birth) *

Mark only one oval.

- ◯ Female
- ◯ Male

8. Age *

_____

9. I am pregnant *

Mark only one oval.

- ◯ Yes
- ◯ No

Question Section #2

Questions about your foot-drop device(s).

10. I regularly use a rigid plastic boot style ankle-foot-orthosis to treat my foot-drop. *

Mark only one oval.

- ◯ Yes, that is correct.
- ◯ No.

11. If you answered 'yes' to the above question, please state your device's manufacturer and model number. If you answered 'no' to the above question, please type 'N/A' below. *

If you do not know the manufacturer or model number, type 'IDK' below.

_____

12. When did you start using your ankle-foot-orthosis? *

If you do not use one, type 'N/A' below.

_____

13. Approximately how many hours per day do you use your ankle-foot-orthosis? *

If you do not use one, type 'N/A' below.

_____

14. I regularly use the (select one of the following) to treat my foot-drop. *

Mark only one oval.

- ◯ WalkAide (made by Innovative Neurotronics)
- ◯ Bioness L300 (the lower leg cuff version made by Bioness Inc.)
- ◯ Neither of the above.
- ◯ Other: _____

15. When did you start using the WalkAide or Bioness L300? *

If you do not use one, type 'N/A' below.

_____

16. Approximately how many hours per day do you use the WalkAide or Bioness L300? *

If you do not use one, type 'N/A' below.

_____

Question Section #3

For reference: 50 meters is approximately 164 feet.

Examples of 50 meters are:
- half the length of a soccer field
- two-and-half bowling lanes
- two-fifths the length of an American football field

17. I can walk 50 meters WITHOUT stopping while using my foot-drop device. (If you have a different distance you know you can walk, please include it in the 'Other' space.) *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] I do NOT experience foot-drop and can walk 50 meters or more just fine.
- [ ] Other: _____

18. I can walk 50 meters WITHOUT a foot-drop device, cane, walker, or other assistive device. (If you have a different distance you know you can walk, please include it in the 'Other' space.) *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] I do NOT experience foot-drop and can walk 50 meters or more just fine.
- [ ] Other: _____

19. Do you use AMPYRA (dalfampridine)? *

Mark only one oval.

- ◯ Yes
- ◯ No

20. If you answered 'yes' to using AMPYRA (dalfampridine), how long have you been using a CONSISTENT dosage? *

Mark only one oval.

- ◯ Less than 30 days
- ◯ More than 30 days
- ◯ I do not take AMPYRA.

17. I can walk 50 meters WITHOUT stopping while using my foot-drop device. (If you have a different distance you know you can walk, please include it in the 'Other' space.) *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] I do NOT experience foot-drop and can walk 50 meters or more just fine.
- [ ] Other: _____

18. I can walk 50 meters WITHOUT a foot-drop device, cane, walker, or other assistive device. (If you have a different distance you know you can walk, please include it in the 'Other' space.) *

Check all that apply.

- [ ] Yes
- [ ] No
- [ ] I do NOT experience foot-drop and can walk 50 meters or more just fine.
- [ ] Other: _____

19. Do you use AMPYRA (dalfampridine)? *

Mark only one oval.

- ◯ Yes
- ◯ No

20. If you answered 'yes' to using AMPYRA (dalfampridine), how long have you been using a CONSISTENT dosage? *

Mark only one oval.

- ◯ Less than 30 days
- ◯ More than 30 days
- ◯ I do not take AMPYRA.

21. When was your last neurological visit?

If you don't remember or do not have multiple sclerosis, leave this blank and move to the next section.

_____

Example: January 7, 2019

Question Section #4

You are almost finished! This is the last set of questions.

22. I have the following (select all that apply): *

Check all that apply.

- [ ] Congestive heart failure
- [ ] Cardiopulmonary disease
- [ ] Uncontrolled diabetes
- [ ] Pressure sores or open wounds
- [ ] A history of epilepsy or seizures
- [ ] Alcoholism
- [ ] Arthritis
- [ ] Healing bone fracture(s)
- [ ] None of the above

23. Do you have any muscular damage that is still healing? Either from an injury or surgery? (If yes, please list it in the 'Other' space.) *

Check all that apply.

- [ ] Yes
- [ ] No

Other: [ ] _____

24. Please select all that apply. *

Check all that apply.

- [ ] I have received cancer treatment within the last 3 months.
- [ ] I am currently participating in another study or clinical trial.

25. Have you experienced the following within the last 3 weeks? *

Mark only one oval.

- ◯ A relapse or exacerbation from your multiple sclerosis.
- ◯ A major physical injury.
- ◯ Both of the above.
- ◯ None of the above.

26. I am NOT a prisoner and do NOT have a warrant, parole, or felony. *

Mark only one oval.

- ◯ Yes
- ◯ No

Appendix D: Participant Data Sheet

The author created the following questionnaire to collect pertinent information for data analysis. The author filled it out with each participant at the beginning of their session. The alphanumeric subject numbers were written within the headers of the pages. Subjects were also asked about the specific types of physical activities they conducted.

Subject #:_____ Basic Subject Data Sheet Date:_____

The following information must be collected for proper data analysis.

1. Foot-drop device: _____
2. When did you start using this foot-drop device? _____
3. Approximately how many hours a day do you use this device? _____
4. You use this device on your (*LEFT / RIGHT*) leg.
5. When were you diagnosed with MS? _____
6. What type of MS do you have? _____
7. PDDS (review Likert sheet with participant): _____
8. Height: _____ feet / m and _____ inches / cm
9. Weight: _____ pounds / kg
10. Age: _____ years
11. Sex (from birth): Female / Male
12. Right Knee Width: _____ inches / millimeters
13. Left Knee Width: _____ inches / millimeters
14. Right Ankle Width: _____ inches / millimeters
15. Left Ankle Width: _____ inches / millimeters
16. Knee Width with assistive device: _____ inches / millimeters
17. Ankle Width with assistive device: _____ inches / millimeters

18. Please estimate your daily and/or weekend physical activity level(s) and describe the intensity.
    Intensity levels descriptions:
    - Easy = normal breathing, could have a conversation or sing
    - Medium = heavy breathing, could have a short conversation but not sing
    - Hard = short of breath, could only speak in short sentences

    a) Hours per **day** spent performing physical activities: _____

    Intensity level of activities: Easy / Medium / Hard

    b) Hours of **recurring weekend** physical activities:_____

    Intensity level of activities: Easy / Medium / Hard

19. Have you experienced any changes since submitting the eligibility questionnaire and scheduling this data collection session?

    Changes in Symptoms/Injury: _____

    _____

    _____

    _____

    Changes in Device or Device Usage: _____

    _____

    _____

    _____

    Changes in Medications or Medication Dosage: _____

    _____

    _____

    _____

Appendix E: Patient-determined Disease Steps (PDDS)

This disability scoring system was developed by NARCOMS and does not require copyright permission, but citation acknowledgement is provided here and in Appendix A.

PDDS: Patient-determined Disease Steps

Please read the choices listed below and choose the one that best describes your own situation.
This scale focuses mainly on how well you walk. You might not find a description that reflects your condition exactly, but please mark the **one** category that describes your situation the closest.

0 – normal
I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.

1 – mild disability
I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.

2 – moderate disability
I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.

3 – gait disability
MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack.

4 – early cane
I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks.

5 – late cane
To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.

6 – bilateral support
To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.

7 – wheelchair / scooter
My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.

8 – bedridden
Unable to sit in a wheelchair for more than one hour.

Appendix F: Motion Capture Marker Set

Motek's 2020 full-body motion capture marker set was used for this dissertation. Motek's 'Full body HBM reference manual' presents an illustration of marker placements on a skeleton with descriptive marker titles and a numbering system. The marker set consists of 46 markers with 22 body segments. Below is the consolidated marker set reference chart the author created for this study. The author provides more clarity by listing the true anatomical positions where markers should be placed on participants.

Table F.1: Anatomical Positions of Full-body Marker Set

Marker Number	Marker Abbreviation [a]	Anatomical Position
1	LHEAD	Left of Head (temple)
2	RHEAD	Right of Head (temple)
3	THEAD	Top of Head (crown)
4	FHEAD	Forehead
5	C7	C7 vertebra
6	T10	T10 vertebra
7	XIPH	Xiphoid Process
8	JN	Jugular Notch
9 / 17	LSHO / RSHO	Shoulder (Acromion)
10 / 18	LDELT / RDELT	Deltoid (Deltoid Tuberosity)
11 /19	LLEE / RLEE	Lateral Epicondyle of Elbow
12 / 20	LMEE / RMEE	Medial Epicondyle of Elbow
13 / 21	LMW / RMW	Medial Wrist (Radial Styloid Process)
14 / 22	LLW / RLW	Lateral Wrist (Ulnar Styloid Process)
15 / 23	LFRM / RFRM	Forearm (Radius)
16 / 24	LFIN / RFIN	Left / Right Finger (Third Metacarpal Head)
25 / 26	LASIS / RASIS	Anterior Superior Iliac Spine
27 / 28	LPSIS / RPSIS	Posterior Superior Iliac Spine
29 / 38	LLTHI / RLTHI	Lateral Thigh (Iliotibial Tract)
30 / 39	LLEK / RLEK	Lateral Epicondyle of Knee (Lateral Epicondyle of Femur)
31 / 40	LMEK / RMEK	Medial Epicondyle of Knee (Medial Epicondyle of Femur)
32 / 41	LLSHA / RLSHA	Lateral Shank (Head of Fibularis Longus Tendon)
33 / 42	LLM / RLM	Lateral Malleolus
34 / 43	LMM / RMM	Medial Malleolus
35 / 44	LHEE / RHEE	Heel (Body of Calcaneus)
36 / 45	LMT2 / RMT2	Second Metatarsal [b] (Second Metatarsal Head)
37 / 46	LMT5 / RMT5	Fifth Metatarsal (Tuberosity of Fifth Metatarsal)

[a] Leading 'L' in marker abbreviations designates left; 'R' designates right.

[b] Marker is actually placed on the big toe (first phalange distal between tuberosity and base).

Appendix G: Full-Body ZYX Marker Template

The Marker Matcher module required a customized file to run properly with Motek's Human Body Model software within the D-Flow program. The author created, from scratch, a single column text file with the ZYX coordinates of all 46 markers. It is saved on the USF D-Flow computer and Box as 'lbb_46mkr_fullbody_HBM.txt.' It is presented here in three columns to keep the presentation concise.

Table G.1: ZYX Reference Coordinates for Marker Matcher Module

46	RLTHI 0.13 0.58 -0.03	FHEAD 0.00 1.54 -0.17
LFIN -0.72 1.30 -0.08	RLEK 0.11 0.43 -0.02	LSHO -0.16 1.35 0.01
RFIN 0.69 1.24 -0.04	RMEK 0.02 0.43 0.00	LDELT -0.32 1.33 -0.01
LASIS -0.15 0.86 -0.11	RLSHA 0.12 .25 0.04	LLEE -0.41 1.32 -0.02
RASIS 0.10 0.86 -0.11	RLM 0.11 0.10 0.07	LMEE -0.41 1.26 -0.06
LPSIS -0.07 0.88 0.04	RMM 0.14 0.10 0.05	LFRM -0.55 1.30 -0.03
RPSIS 0.04 0.89 0.05	RHEE 0.08 0.06 0.12	LLW -0.65 1.27 -0.04
LLTHI -0.18 0.58 0.03	RMT2 0.12 0.05 -0.11	LMW -0.65 1.27 -0.10
LLEK -0.17 0.45 -0.03	RMT5 0.15 0.04 -0.02	RSHO 0.12 1.33 0.01
LMEK -0.10 0.43 -0.02	C7 -0.01 1.35 0.03	RDELT 0.27 1.30 0.00
LLSHA -0.19 .27 0.03	T10 -0.02 1.10 0.07	RLEE 0.38 1.29 0.00
LLM -0.19 0.10 0.08	XIPH -0.02 1.10 -0.13	RMEE 0.38 1.23 -0.07
LMM -0.12 0.11 0.05	JN -0.02 1.26 -0.08	RFRM 0.50 1.27 -0.01
LHEE -0.15 0.07 0.12	LHEAD -0.07 1.54 -0.11	RLW 0.62 1.22 -0.02
LMT2 -0.22 0.06 -0.10	THEAD -0.02 1.62 -0.02	RMW 0.60 1.23 -0.10
LMT5 -0.25 0.05 -0.04	RHEAD 0.05 1.53 -0.14	

Appendix H: Borg 6-20 Ratings of Perceived Exertion Form

The original scale was created by Borg in 1982 and has since been supplied by the CDC. There are also various adaptions to the language depending on the source, but it remains largely unchanged. Below is the Borg 6-20 questionnaire that was presented to participants after they completed each multimodal walking trial. In the header space, the alphanumeric subject number and trial type (aided/unaided) were recorded.

Subject #: _____ Trial Type: *Aided / Unaided* Date: _____

Please circle one rating that best describes the level of exertion you experienced during your gait trial.

Perceived Exertion	Rating
No exertion	6
Extremely light	7
	8
Very light	9
	10
Light	11
	12
Somewhat hard	13
	14
Hard	15
	16
Very hard	17
	18
Extremely hard	19
Maximal exertion	20

* Table based on a scale originally created by Borg, G.A. (1982). Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982: 14: 377– 381.
** Most recent publication discussing the scale: Williams, N. The Borg Rating of Perceived Exertion (RPE) scale. *Occup Med* 2017; 67: 404–405.

Appendix I: 7-point Likert Scale for Walking Confidence

The author created the following walking confidence questionnaire and presented it to participants after they completed each multimodal walking trial. In the header space, the alphanumeric subject number and trial type (aided/unaided) were recorded.

Subject #: _____ Trial Type: *Aided / Unaided* Date: _____

Check one of the following that best describes your level of walking confidence during your gait trial:

- ☐ Very confident
- ☐ Confident
- ☐ Somewhat confident
- ☐ Neither confident nor unconfident (neutral)
- ☐ Somewhat unconfident
- ☐ Unconfident
- ☐ Very unconfident

Appendix J: Data Summary Tables

Table J.1: Controls' Mobility Parameters via GOAT
(Mean with standard deviation over entire multimodal trial)

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
control_01	0.91 ± 0.20	101 ± 7	0.09 ± 0.03	0.55 ± 0.07	1.09 ± 0.14	0.60 ± 0.04	1.19 ± 0.08	0.80 ± 0.07	0.39 ± 0.02	32.62 ± 2.33	34.37 ± 2.77
control_02	1.28 ± 0.17	111 ± 6	0.11 ± 0.03	0.70 ± 0.07	1.39 ± 0.13	0.54 ± 0.03	1.08 ± 0.04	0.71 ± 0.03	0.37 ± 0.02	34.34 ± 2.46	31.24 ± 2.78
control_03	0.78 ± 0.20	93 ± 7	0.21 ± 0.03	0.51 ± 0.09	1.02 ± 0.17	0.65 ± 0.05	1.29 ± 0.08	0.89 ± 0.08	0.40 ± 0.04	31.07 ± 2.28	37.89 ± 4.33
control_04	1.14 ± 0.21	122 ± 6	0.18 ± 0.03	0.57 ± 0.08	1.13 ± 0.15	0.49 ± 0.03	0.98 ± 0.05	0.66 ± 0.04	0.33 ± 0.02	33.22 ± 1.47	33.48 ± 2.43
control_05	0.88 ± 0.15	97 ± 6	0.12 ± 0.02	0.55 ± 0.06	1.10 ± 0.11	0.62 ± 0.05	1.24 ± 0.05	0.83 ± 0.05	0.41 ± 0.02	32.72 ± 2.17	34.33 ± 3.01
control_06	1.11 ± 0.18	102 ± 5	0.16 ± 0.03	0.65 ± 0.06	1.30 ± 0.12	0.59 ± 0.03	1.17 ± 0.04	0.78 ± 0.06	0.39 ± 0.04	32.84 ± 2.74	33.48 ± 3.00
control_07	1.10 ± 0.20	115 ± 15	0.16 ± 0.04	0.59 ± 0.08	1.17 ± 0.14	0.53 ± 0.05	1.05 ± 0.06	0.69 ± 0.05	0.36 ± 0.03	34.27 ± 1.84	31.40 ± 3.42
control_08	0.90 ± 0.16	106 ± 7	0.09 ± 0.02	0.52 ± 0.07	1.03 ± 0.13	0.57 ± 0.03	1.14 ± 0.05	0.76 ± 0.04	0.38 ± 0.02	33.43 ± 2.23	33.21 ± 2.75
control_09	1.24 ± 0.17	112 ± 6	0.12 ± 0.03	0.66 ± 0.04	1.33 ± 0.08	0.54 ± 0.03	1.07 ± 0.05	0.71 ± 0.05	0.37 ± 0.01	34.06 ± 1.31	31.79 ± 2.12
control_10	0.93 ± 0.15	97 ± 5	0.15 ± 0.02	0.58 ± 0.05	1.15 ± 0.09	0.62 ± 0.03	1.24 ± 0.05	0.84 ± 0.05	0.40 ± 0.02	32.14 ± 1.10	35.73 ± 1.62
control_11	1.06 ± 0.19	116 ± 19	0.15 ± 0.02	0.57 ± 0.08	1.13 ± 0.16	0.52 ± 0.05	1.06 ± 0.04	0.71 ± 0.05	0.35 ± 0.04	33.40 ± 4.47	33.66 ± 4.56
control_12	1.06 ± 0.16	105 ± 4	0.18 ± 0.03	0.61 ± 0.05	1.21 ± 0.09	0.57 ± 0.02	1.14 ± 0.04	0.77 ± 0.03	0.38 ± 0.02	32.78 ± 2.11	34.12 ± 2.35
control_13	1.10 ± 0.16	90 ± 6	0.19 ± 0.03	0.74 ± 0.04	1.48 ± 0.07	0.67 ± 0.04	1.34 ± 0.05	0.89 ± 0.05	0.45 ± 0.03	33.96 ± 2.89	32.31 ± 3.42
control_group	1.04 ± 0.15	105 ± 10	0.15 ± 0.04	0.60 ± 0.07	1.19 ± 0.14	0.58 ± 0.05	1.15 ± 0.10	0.77 ± 0.08	0.38 ± 0.03	33.14 ± 0.93	33.62 ± 1.82

Table J.2: pwMS's Mobility Parameters via GOAT
(Mean with standard deviation over entire multimodal trial)

Participant	Walking Speed (m/s)	Cadence (steps/min)	Step Width (m)	Step Length (m)	Stride Length (m)	Step Time (s)	Stride Time (s)	Stance Time (s)	Swing Time (s)	Single Support % (total per leg)	Total Double Support %
AFO-user_01* (Unaided)	0.93 ± 0.16	130 ± 15	0.13 ± 0.03	0.44 ± 0.06	0.87 ± 0.10	0.47 ± 0.05	0.94 ± 0.06	0.63 ± 0.05	0.31 ± 0.02	32.78 ± 1.63	34.35 ± 2.44
AFO-user_01* (Ottobock)	0.97 ± 0.13	128 ± 12	0.12 ± 0.02	0.46 ± 0.05	0.91 ± 0.08	0.47 ± 0.04	0.95 ± 0.05	0.64 ± 0.04	0.31 ± 0.02	32.90 ± 1.63	34.18 ± 1.99
AFO-user_02 (Unaided)	0.48 ± 0.14	100 ± 14	0.22 ± 0.02	0.31 ± 0.07	0.62 ± 0.13	0.61 ± 0.09	1.25 ± 0.07	0.94 ± 0.08	0.31 ± 0.05	25.96 ± 2.03	49.42 ± 3.55
AFO-user_02 (Ottobock)	0.72 ± 0.19	103 ± 13	0.19 ± 0.02	0.43 ± 0.08	0.85 ± 0.15	0.60 ± 0.11	1.16 ± 0.07	0.83 ± 0.10	0.34 ± 0.13	26.41 ± 4.89	44.76 ± 7.25
AFO-user_03 (Unaided)	1.04 ± 0.26	112 ± 20	0.08 ± 0.03	0.59 ± 0.11	0.16 ± 0.20	0.55 ± 0.09	1.08 ± 0.07	0.71 ± 0.09	0.37 ± 0.08	33.90 ± 7.12	31.79 ± 8.40
AFO-user_03 (Ottobock)	1.21 ± 0.23	116 ± 14	0.08 ± 0.02	0.65 ± 0.07	1.29 ± 0.11	0.53 ± 0.07	1.04 ± 0.07	0.68 ± 0.07	0.36 ± 0.04	35.02 ± 4.31	30.27 ± 5.44
AFO-user_04* (Hinged)	1.14 ± 0.13	128 ± 15	0.10 ± 0.03	0.54 ± 0.06	1.08 ± 0.08	0.48 ± 0.06	0.95 ± 0.05	0.62 ± 0.04	0.32 ± 0.03	34.01 ± 2.35	31.79 ± 2.24
FES-user_01* (WalkAide)	1.07 ± 0.13	122 ± 15	0.09 ± 0.04	0.53 ± 0.05	1.06 ± 0.07	0.50 ± 0.06	1.00 ± 0.06	0.67 ± 0.05	0.33 ± 0.02	33.21 ± 1.53	33.50 ± 1.81
AFO_group (Unaided)	0.82 ± 0.30	114 ± 15	0.14 ± 0.07	0.45 ± 0.14	0.55 ± 0.36	0.54 ± 0.07	1.09 ± 0.16	0.76 ± 0.16	0.33 ± 0.03	30.88 ± 4.30	38.52 ± 9.53
AFO_group (Aided)	1.01 ± 0.22	118 ± 12	0.12 ± 0.05	0.52 ± 0.10	1.03 ± 0.20	0.52 ± 0.06	1.03 ± 0.10	0.69 ± 0.10	0.33 ± 0.02	32.09 ± 3.88	35.25 ± 6.54

*Case study participant who completed three sessions separated by several weeks.

Table J.3: Controls' Symmetry Parameters via GOAT
(Mean with standard deviation over entire multimodal trial)

Participant / Parameter	Step Length (m)		Step Time (s)		Stance Time (s)		Swing Time (s)		Stance %		Swing %		Single Support %	
	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg
control_01	0.54 ± 0.09	0.55 ± 0.05	0.60 ± 0.05	0.60 ± 0.04	0.80 ± 0.07	0.80 ± 0.06	0.40 ± 0.03	0.39 ± 0.02	66.61 ± 1.84	67.33 ± 1.48	33.39 ± 1.84	32.67 ± 1.48	31.96 ± 2.69	33.23 ± 1.76
control_02	0.71 ± 0.07	0.68 ± 0.07	0.54 ± 0.02	0.54 ± 0.03	0.71 ± 0.03	0.72 ± 0.03	0.38 ± 0.02	0.37 ± 0.01	65.33 ± 1.34	65.83 ± 1.13	34.67 ± 1.34	34.17 ± 1.13	33.89 ± 1.20	34.79 ± 3.23
control_03	0.52 ± 0.09	0.50 ± 0.09	0.64 ± 0.05	0.66 ± 0.05	0.90 ± 0.09	0.88 ± 0.08	0.39 ± 0.05	0.41 ± 0.03	69.50 ± 3.68	68.40 ± 2.34	30.50 ± 3.68	31.60 ± 2.34	31.41 ± 2.22	30.71 ± 2.30
control_04	0.59 ± 0.06	0.55 ± 0.08	0.49 ± 0.02	0.50 ± 0.03	0.66 ± 0.04	0.65 ± 0.04	0.32 ± 0.01	0.33 ± 0.02	67.08 ± 1.20	66.35 ± 1.66	32.92 ± 1.20	33.65 ± 1.66	33.79 ± 0.97	32.68 ± 1.65
control_05	0.54 ± 0.05	0.57 ± 0.07	0.63 ± 0.03	0.61 ± 0.06	0.82 ± 0.04	0.84 ± 0.05	0.42 ± 0.02	0.40 ± 0.02	66.34 ± 1.17	67.80 ± 1.85	33.66 ± 1.17	32.20 ± 1.85	32.24 ± 1.67	33.23 ± 2.51
control_06	0.65 ± 0.08	0.65 ± 0.04	0.58 ± 0.04	0.59 ± 0.02	0.77 ± 0.07	0.78 ± 0.04	0.39 ± 0.05	0.39 ± 0.01	66.26 ± 5.46	66.57 ± 1.10	33.74 ± 5.46	33.43 ± 1.10	32.68 ± 3.78	33.00 ± 0.88
control_07	0.57 ± 0.08	0.61 ± 0.07	0.52 ± 0.05	0.53 ± 0.05	0.68 ± 0.06	0.69 ± 0.05	0.36 ± 0.03	0.36 ± 0.03	65.28 ± 2.27	66.04 ± 2.15	34.72 ± 2.27	33.96 ± 2.15	33.94 ± 1.33	34.59 ± 2.19
control_08	0.50 ± 0.06	0.54 ± 0.07	0.56 ± 0.04	0.58 ± 0.03	0.76 ± 0.04	0.76 ± 0.04	0.38 ± 0.01	0.38 ± 0.02	66.87 ± 1.34	66.40 ± 1.77	33.13 ± 1.34	33.60 ± 1.77	33.79 ± 2.79	33.06 ± 1.36
control_09	0.66 ± 0.05	0.67 ± 0.04	0.54 ± 0.03	0.53 ± 0.03	0.71 ± 0.05	0.71 ± 0.04	0.37 ± 0.01	0.37 ± 0.02	65.88 ± 1.40	65.81 ± 1.30	34.12 ± 1.40	34.19 ± 1.30	34.14 ± 1.26	33.98 ± 1.35
control_10	0.58 ± 0.05	0.57 ± 0.05	0.61 ± 0.03	0.63 ± 0.03	0.85 ± 0.05	0.84 ± 0.05	0.39 ± 0.02	0.40 ± 0.02	68.22 ± 1.20	67.52 ± 1.09	31.78 ± 1.20	32.48 ± 1.09	32.47 ± 1.00	31.82 ± 1.09
control_11	0.56 ± 0.09	0.58 ± 0.07	0.52 ± 0.05	0.52 ± 0.04	0.71 ± 0.04	0.71 ± 0.05	0.35 ± 0.03	0.35 ± 0.04	67.09 ± 3.05	67.02 ± 3.61	32.91 ± 3.05	32.98 ± 3.61	33.61 ± 5.45	33.17 ± 3.13
control_12	0.61 ± 0.06	0.60 ± 0.03	0.57 ± 0.03	0.58 ± 0.02	0.77 ± 0.03	0.77 ± 0.03	0.37 ± 0.02	0.38 ± 0.01	67.27 ± 1.75	67.06 ± 0.96	32.73 ± 1.75	32.94 ± 0.96	32.72 ± 2.81	32.84 ± 0.94
control_13	0.72 ± 0.04	0.75 ± 0.04	0.66 ± 0.04	0.67 ± 0.04	0.89 ± 0.05	0.89 ± 0.05	0.45 ± 0.03	0.45 ± 0.03	66.36 ± 2.32	66.19 ± 2.25	33.64 ± 2.32	33.81 ± 2.25	34.00 ± 3.02	33.93 ± 2.78
control_group	0.60 ± 0.07	0.60 ± 0.07	0.57 ± 0.05	0.58 ± 0.05	0.77 ± 0.08	0.77 ± 0.08	0.38 ± 0.03	0.38 ± 0.03	66.78 ± 1.15	66.79 ± 0.80	33.22 ± 1.15	33.18 ± 0.80	33.13 ± 0.91	33.16 ± 1.09

Table J.4: pwMS's Symmetry Parameters via GOAT
(Mean with standard deviation over entire multimodal trial)

Participant / Parameter	Step Length (m)		Step Time (s)		Stance Time (s)		Swing Time (s)		Stance %		Swing %		Single Support %	
	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg	Left Leg	Right Leg
AFO-user_01* (Unaided)	0.45 ± 0.06	0.43 ± 0.06	0.43 ± 0.04	0.51 ± 0.03	0.63 ± 0.05	0.63 ± 0.05	0.30 ± 0.02	0.31 ± 0.02	67.64 ± 1.37	66.64 ± 1.47	32.36 ± 1.37	33.36 ± 1.47	33..57 ± 1.56	32.03 ± 1.30
AFO-user_01* (Ottobock)	0.47 ± 0.05	0.45 ± 0.04	0.44 ± 0.03	0.51 ± 0.02	0.64 ± 0.04	0.63 ± 0.04	0.30 ± 0.02	0.32 ± 0.01	67.85 ± 1.31	66.32 ± 1.22	32.15 ± 1.31	33.68 ± 1.22	33.93 ± 1.34	31.88 ± 1.20
AFO-user_02 (Unaided)	0.32 ± 0.08	0.30 ± 0.07	0.69 ± 0.06	0.55 ± 0.03	0.92 ± 0.07	0.97 ± 0.08	0.33 ± 0.04	0.29 ± 0.05	73.64 ± 2.88	76.91 ± 4.36	26.36 ± 2.88	23.09 ± 4.36	25.07 ± 0.92	26.74 ± 2.45
AFO-user_02 (Ottobock)	0.45 ± 0.05	0.40 ± 0.10	0.63 ± 0.07	0.56 ± 0.13	0.81 ± 0.05	0.84 ± 0.14	0.36 ± 0.07	0.31 ± 0.17	69.55 ± 4.06	73.21 ± 11.77	30.45 ± 4.06	26.79 ± 11.77	24.68 ± 3.32	28.13 ± 5.60
AFO-user_03 (Unaided)	0.64 ± 0.06	0.51 ± 0.13	0.59 ± 0.08	0.50 ± 0.08	0.67 ± 0.08	0.76 ± 0.08	0.41 ± 0.06	0.31 ± 0.07	62.22 ± 5.31	70.79 ± 6.18	37.78 ± 5.31	29.21 ± 6.18	31.03 ± 5.30	38.13 ± 7.46
AFO-user_03 (Ottobock)	0.68 ± 0.06	0.61 ± 0.05	0.54 ± 0.06	0.50 ± 0.07	0.66 ± 0.07	0.71 ± 0.06	0.37 ± 0.04	0.35 ± 0.02	63.88 ± 4.24	67.09 ± 1.81	36.12 ± 4.24	32.91 ± 1.81	34.01 ± 2.23	36.30 ± 5.78
AFO-user_04* (Hinged)	0.58 ± 0.03	0.50 ± 0.06	0.43 ± 0.03	0.52 ± 0.03	0.63 ± 0.04	0.62 ± 0.04	0.31 ± 0.02	0.34 ± 0.02	67.15 ± 1.30	64.48 ± 1.62	32.85 ± 1.30	35.52 ± 1.62	35.82 ± 1.88	32.23 ± 1.30
FES-user_01* (WalkAide)	0.56 ± 0.04	0.51 ± 0.04	0.45 ± 0.03	0.55 ± 0.03	0.67 ± 0.05	0.65 ± 0.05	0.32 ± 0.02	0.34 ± 0.02	67.67 ± 1.27	65.72 ± 1.31	32.33 ± 1.27	34.28 ± 1.31	34.29 ± 1.16	32.10 ± 0.97
AFO_group (Unaided)	0.47 ± 0.16	0.41 ± 0.11	0.57 ± 0.13	0.52 ± 0.03	0.74 ± 0.16	0.79 ± 0.17	0.35 ± 0.06	0.30 ± 0.01	67.83 ± 5.71	71.45 ± 5.17	32.17 ± 5.71	28.55 ± 5.17	29.89 ± 4.36	32.30 ± 5.70
AFO_group (Aided)	0.55 ± 0.11	0.49 ± 0.09	0.51 ± 0.09	0.52 ± 0.03	0.69 ± 0.08	0.70 ± 0.10	0.34 ± 0.04	0.33 ± 0.02	67.11 ± 2.38	67.78 ± 3.79	32.89 ± 2.38	32.23 ± 3.79	32.11 ± 5.03	32.14 ± 3.34

*Case study participant who completed three sessions separated by several weeks.

About the Author

Prior to pursuing her Biomedical Engineering Doctorate, Laura Byrnes-Blanco studied mechanical engineering and business. After two consecutive undergraduate internships at the National Institute of Standards and Technology, she was inspired to pursue a doctorate. Whether her next steps are in industry or academia, she will continue to pursue and value collaborative, multidisciplinary projects while continuing to prioritize honesty, integrity, and purpose in her work.