



Post-Stroke Walking Speed and Community Ambulation Conversion, A Pivotal Study

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STUDY SYNOPSIS

Study Sponsor	MedRhythms, Inc., 183 Middle Street, Suite 300, Portland, Maine 04101
Protocol Number	PS100
Investigational Device	<u>Device Name:</u> MedRhythm's <i>Stride Plus</i> The MedRhythms <i>Stride Plus</i> includes a patient application and sensors with commercially available headphones and smartphones. The <i>Stride Plus</i> is a device intended to improve gait metrics in the chronic stroke population, with the goal of converting limited ambulators to community ambulators, by improving walking speed. It is also intended to track patient progress, and facilitate communication between patients, caregivers and clinicians. This technology uses Rhythmic Auditory Stimulation - embedded audio cues to facilitate improvements in walking speed. When using the system, patients walk with sensors that are attached to their shoes and collect gait parameters, including the following measurements: speed, stride length, symmetry (temporal and spatial), and cadence. When marketed, clinicians will be able to pre-program the device with the patients' rehabilitation goals, and the algorithm uses these endpoints and feedback from the sensors to inform changes made to the audio cues. These cues, which are embedded in time-shifted music, are delivered back to the users who aim to walk to the beat. Research shows that walking to an external rhythmic stimulus globally engages the brain, coupling the auditory and motor regions. For stroke survivors with damage to the motor system, this dual engagement has the effect of establishing new neural connections to the motor region. Furthermore, this has the potential to make walking certain distances, which may ordinarily be onerous or impossible tasks, achievable for these individuals. As a result of neuroplasticity, repeating these audio-cueing exercises on a consistent basis can change one's brain composition, allowing walking improvements made with the device to manifest without the engagement of the intervention.
Primary Objective	The purpose of this clinical study is to demonstrate that after five weeks of training at three times per week with <i>Stride Plus</i> , participants representing limited community ambulators in the chronic stroke population will on average have increased their walking speed more than the active control group as measured

	by the 10 Meter Walk test. Additionally, the gait speed increase will be greater than the MCID of .15m/s. ^{1,2}
Secondary Objectives	1. To demonstrate that after five weeks of training with <i>Stride Plus</i>, a larger proportion of participants in the intervention group will become community ambulators compared to the active control group. a. Additionally, the proportion of participants who achieve a minimum 0.15 m/s change in gait speed <i>and</i> convert to community ambulator status will be greater in the <i>Stride Plus</i> group. 2. To show that the changes in Cadence, Stride Length, Temporal Symmetry, and Spatial Symmetry as measured by an instrumented walkway system at the completion of study participation are improved with <i>Stride Plus</i>. a. There will be a positive correlation among these measures with those from the sensors of the Stride Plus. b. No relationship will be seen on a Bland-Altman plot. 3. Quality life and self-perceived disability, as measured at the closing visit will have greater improvement in the <i>Stride Plus</i> group. 4. There will be no significant differences in safety or adverse outcomes between groups.
Primary Endpoint	The primary outcomes will be the mean increase in gait speed (m/s) and mean percent increase in gait speed as determined by a 10-meter Walk Test after five weeks of training and compared between groups.
Study Population	<u>Target Age:</u> Patients 50 years of age and older are eligible to participate (see Inclusion Criteria below). This target age was chosen in order to minimize potential bias by recruitment of younger stroke patients, shown to have better functional recoveries.³ <u>Race/Ethnicity:</u> All races and ethnicities are eligible to be enrolled. <u>Education Level:</u> All educational levels will be enrolled, e.g., no high school diploma, those with a GED or high school diploma, those with some college, those with a bachelor's degree and those with advanced degrees. <u>Geographic Diversity:</u>

¹ Lewek, M. D., PhD, & Sykes, R., III. (2018). Minimal Detectable Change for Gait Speed Depends on Baseline Speed in Individuals With Chronic Stroke. *Journal of Neurologic Physical Therapy*. doi:10.1097/NPT.0000000000000257

² Bohannon, R. W., & Glenney, S. S. (2014). Minimal clinically important difference for change in comfortable gait speed of adults with pathology: A systematic review. *Journal of Evaluation in Clinical Practice*, 20(4), 295-300. doi:10.1111/jep.12158

³ Putaala, J., MD. (2017). *Defining Young Stroke*. Manuscript. Retrieved from <http://youngstroke.org/wp-content/uploads/2017/04/DefiningYoungStroke.pdf>

	Enrollment is expected to achieve a full representation of geographic diversity in the United States (urban, suburban, rural) through a multi-site approach.
Inclusion Criteria	Potential Study Subjects meeting <i>all</i> of the following inclusion criteria: 1.0 50 years of age and older 2.0 Equal to or greater than six months post-stroke, as determined by past medical history review 3.0 Currently able to walk at a speed greater or equal to 0.5m/s, but less than 0.8m/s, as determined by a 10-meter walk test for comfortable walking speed (the average of three trials) without using assistive devices⁴. 4.0 Demonstrates some level of asymmetry in gait 5.0 Able and willing to consent with proposed study schema (verbal commitment), including consent to participate in communication with the treating clinician (as needed) during the study period 6.0 Score ≤ 1 on question 1b and a 0 on question 1c on the NIH Stroke Scale 7.0 Able to safely participate in protocol-defined walking therapy sessions of 30 minute duration as determined by the Investigator.
Exclusion Criteria	Any Study Subject who does not meet <i>all</i> of the above inclusion criteria will be excluded from the clinical study. In addition, any Study Subject that meets the following criteria will <i>also</i> be excluded from study enrollment. 1.0 Subject is currently enrolled in study to evaluate an investigational drug. 2.0 Subject has already participated in this study. 3.0 Subject unable or unwilling to provide informed consent. 4.0 Subject is unable to participate in protocol-defined walking therapy sessions of 30-minute duration without the use of assistive devices⁴ as determined by Subject and Principal Investigator. 5.0 Subject is considered a community ambulator (walking speed ≥ 0.8 m/s) when not using an assistive device⁴ as determined by a 10-meter walk test for comfortable walking speed (the average of three trials). 6.0 Has a known history of neurologic (excluding stroke) injury, as determined by past medical history review 7.0 Has had more than 2 falls in the previous month, as determined by patient self-report 8.0 Is enrolled in another walking rehabilitation intervention (e.g., physical therapy) 9.0 Has an external lower limb prosthetic ("artificial limb"), as determined by patient self-report

⁴ Assistive devices are defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted.

	10.0 Has a hearing impairment, as determined by past medical history review 11.0 Had orthopedic surgery in the last year, as determined by past medical history review 12.0 Has severe aphasia and/or a speech/language disorder, limiting ability to express needs and comprehend instructions, as determined by past medical history review 13.0 Has co-morbidities that prevent participation in exercise, as determined by past medical history review (for example: musculoskeletal, cardiovascular, pulmonary and neurological – other than stroke) 14.0 Vulnerable populations as deemed inappropriate for study by site Principal Investigator.
Prospective Study Design	This study will be a multi-site, prospective, randomized controlled clinical study. The study will be performed at a minimum of three (3) rehabilitation centers, hospitals, or academic facilities under the supervision of study staff. Each site will randomize participants at their location to cohorts using block randomization with randomly selected block sizes. Approximately eighty Subjects (n=78) will be prospectively enrolled. Each site will target enrollment of 26 Subjects. Additional Subjects may be enrolled after authorization from the Sponsor. All interested, potential subjects will participate in the following study phase: 1) <u>Screening</u>: A study visit intended for execution of the informed consent form and collection of baseline data for eligibility. Individuals who qualify for enrollment per the inclusion/exclusion criteria will be notified and participate in the following study phases: 2) <u>Enrollment</u>: Confirmation of eligibility and randomization (no study visit required). Upon enrollment, patients will be randomized into one of two cohorts: <u>Cohort A</u>: <i>Stride Plus</i> Intervention Arm <u>Cohort B</u>: Active Walking Intervention Arm All Study Subject's will be provided a schedule of intervention visits at this time. 3) <u>Intervention</u>: A series of fifteen (15) study visits intended to collect data toward study objectives 4) <u>Post-Intervention</u>: A single study visit intended to collect post-intervention data to measure change from baseline. <u>Cohort A: Stride Plus</u> will use the <i>Stride Plus</i>, headphones and sensors for 30 minutes at a time, 3 times a week, for 5 weeks and perform the 10-meter walk

	tests. Each session will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions. <u>Cohort B: Active Control</u> will walk 30 minutes at a time with the <i>Stride Plus</i> sensors only, 3 times a week, for 5 weeks and perform the 10-meter walk tests. Each session will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. No mobile devices, music players or headphones will be used. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions. The 10-meter walk test will be conducted twice per session, once at the beginning and once at the end. Physiological measurements will be taken at each study visit and abide by the Institution's standard procedures to ensure safety of the participants. Biomechanical, cognitive and stroke specific Quality of Life (ss-QoL) measurements will be taken only at the screening and post-intervention phase. Photos or videos may be taken as Study Subjects complete research activities to allow offline analyses by investigators who were not at study visits and for use in publications or presentations. All video and photographic data that is taken will not contain any Study Subject names and will be stored on a password protected server with access limited to study staff. Every attempt will be made to avoid capturing participants' faces. Each Subject's data will be recorded on source documentation and entered into electronic Case Report Forms (eCRFs). Data collected from the sensors used in both cohorts may be used for future product development, product clearance/registration and/or product improvement. This study will be listed on clinical trials.gov. Therefore, results will be published per FDA requirements.
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Prospective Study Sample Size	The study is powered for the primary outcomes, gait speed and percent change in Gait speed. Statistical power was set at 80% and the overall two-tailed alpha-level was set at .05. Approximately 78 participants will be prospectively enrolled at a minimum of three (3) sites with a target of 26 participants per site. Allowing for 15% attrition and instrument failure, it is expected that 66 participants will complete the study, 33 in each group and 22 at each site. Subjects will continue to be enrolled until the targeted number of endpoints have been reached. When sufficient data has been collected to evaluate device performance, continued enrollment into the study will be assessed. The Sponsor retains the right to halt enrollment in the study when sufficient data has been collected to support the objectives of this study. <u>Statistical Considerations due to COVID-19:</u> Due to the COVID-19 public health emergency, on March 17, 2020, study activities were put on hold due to mandates from the participating research institutions. The Sponsor engaged a consulting statistician to perform an unplanned, interim analysis. The interim analyses assessed the effectiveness of device with the data collected prior to the health emergency, allowing for an estimate of the observed effect. Considering the intended user population being at a far greater risk to complications from COVID-19^{5,6,7,8}, and when research activities for the study are able to resume at the participating institutions, the Sponsor intends to implement a newly planned interim analysis when a total of forty (40) participants are randomized into the study, which is approximately half of the anticipated enrollment. The interim analysis will follow the analysis plan as outlined in section 13.1; however, alpha will be set to 0.0125 for the primary outcomes. Due to the unplanned analysis, the original alpha of .05 was adjusted by half (0.025). The remaining 0.025 to be split between the newly planned interim analysis and the original final analysis. This adjustment is a conservative attempt to control for type I error inflation. If significance is found in the planned interim analysis that supports the objectives of this study, the Sponsor may use the results to support regulatory authorization to market the device. Additionally, the Sponsor intends to perform a poolability analysis to assess the comparability of patients enrolled before and after this trial modification. If those recruited after March 17, 2020 differ from those already collected, a pre vs. post COVID-19 variable will be included in the models to adjust for the difference. All study staff involved in the conduct of the trial will remain blinded to results of the interim analysis to ensure the trial conduct will not be affected by the results.
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Duration of Prospective Subject Participation	All key assessments points and interventions will be conducted at a study site. The screening visit and closing visit are expected to take up to three (3) hours. Training visits are expected to take one and half (1.5) hours. In total, study participation is expected to occur over 6 weeks.
Study Duration	Approximately six (6) months, starting mid-2019.

⁵ <https://publichealth.jmir.org/2020/2/e19462/#ref10>. Considerations for Postacute Rehabilitation for Survivors of COVID-19

⁶ <http://europepmc.org/article/MED/32194034>. How Should the Rehabilitation Community Prepare for 2019-nCoV?

⁷ <https://www.sciencedaily.com/releases/2020/05/200521124648.htm>. Stroke rates among COVID-19 patients are low, but cases are more severe

⁸ https://www.nejm.org/doi/full/10.1056/NEJMc2009787?query=featured_home. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

ABBREVIATIONS

AE	Adverse Event
BP	Blood Pressure
BPM	Beats per Minute
CFR	Code of Federal Regulations
DBP	Diastolic Blood Pressure
FDA	Food and Drug Administration
GLMM	General Linear Mixed Model
HIPAA	Health Insurance Portability and Accountability Act
hr	Hour
HR	Heart Rate
Hx	History
ICH	International Conference on Harmonization
IRB	Institutional Review Board
km	kilometers
m	meters
mmHg	Millimeter of Mercury
MCID	Minimal Clinically Important Difference
MWT	Meter Walk Test
NMT	Neurologic Music Therapy
PI	Principal Investigator
RAS	Rhythmic Auditory Stimulation
s	Second
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
ss-QoL	Stroke-specific Quality of Life

1 BACKGROUND

Current literature indicates that chronic stroke walking deficits increase fall risk, reduce quality of life, and significantly lower levels of independence. In the U.S., 3.3MM, or 47%, of the 7MM stroke survivors suffer from post-stroke walking impairments, and this number increases by 333K every year.⁹

Notwithstanding the implications of chronic stroke gait deficits on the lives of patients and the costs to the healthcare industry, there is currently no standard of care for the chronic stroke population. According to the "Guidelines for Adult Stroke Rehabilitation and Recovery," stroke patients in the US experience "the end of formal rehabilitation ... 3-4 months after stroke"¹⁰.

The phases of stroke recovery and the associated rehabilitation standards are delineated in the following table:

Figure 1: Post-Stroke Continuum of Care

Stroke Stage	Acute	Post-Acute	Chronic
Length of Stage	Days	Months	Years (often entire life)
Length of Formal Care/Rehabilitation Program	4 Days	3-4 Months	No formal program
Care/Rehabilitation Guidelines	Stabilization of patient and, in cases of ischemic stroke, t-PA may be administered within 3 hours of onset (Wissel et. al, 2013); formal rehab assessment prior to discharge to an IRF, SNF, or home (Stroke Guidelines)	Intensity of rehab varies based on patient functioning levels and discharge location; Minimum of 20 mins aerobic exercise 3 days per week for 8 weeks, along with lighter exercise on the other days of the week (Stroke Guidelines)	None

This is the part of the post-stroke care continuum that MedRhythms seeks to address with Stride Plus




Stroke phases can be broken into three categories, which are, in chronological order, the "acute," "subacute," and "chronic" phases. While the acute and subacute phases of stroke progression occur in the first six months post-stroke, "the chronic phase begins months to years after stroke, and it may continue for the remainder of the person's life"¹¹. Healthcare institutions and clinicians have identified that the paucity of rehabilitation solutions for the chronic stroke population is a flaw in the current system that needs to be addressed. The most recent version of the *Stroke Guidelines* for clinicians

⁹ American Stroke Association. 2018. <http://www.strokeassociation.org/STROKEORG/>.

¹⁰ Winstein, Carolee J. et al. "Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association." *Stroke*. 2016.

¹¹ Kiran, Swathi. "What Is the Nature of Poststroke Language Recovery and Reorganization?" *ISRN Neurology*. 2012.

emphasized the importance and lack of “effective models of care that consider stroke as a chronic condition rather than simply a single acute event”¹⁰.

According to the *Stroke Guidelines*, clinicians regard walking speed as a critical rehabilitation endpoint because it is correlated with fall risk. Moreover, the guidelines indicate that falls in post-stroke populations are most commonly caused by gait limitations and are significantly more likely to result in serious injury or repeated falls¹⁰. These guidelines also highlight that clinicians consider the minimum average speed required for community ambulation, or “independent mobility outside the home,” to be at or above 0.8 m/s.¹⁰ In contrast, walking speeds below 0.8 m/s and above 0.4 m/s are associated with limited community ambulation¹⁰. While the average elderly walking speed is 1.3 m/s¹², the average chronic stroke gait speed is 0.74 m/s.¹³ This suggests that the average chronic stroke patient is not a community ambulator, but 74.6% of stroke patients regard community ambulation “as either essential or very important” to their wellbeing.¹³ Numerous publications corroborate this connection between community ambulation and quality of life.¹⁴

Figure 2 illustrates the correlations between walking speed ranges (i.e. category of ambulation) and clinically meaningful variables: dependence, hospitalization, rehabilitation needs and discharge locations.¹⁵

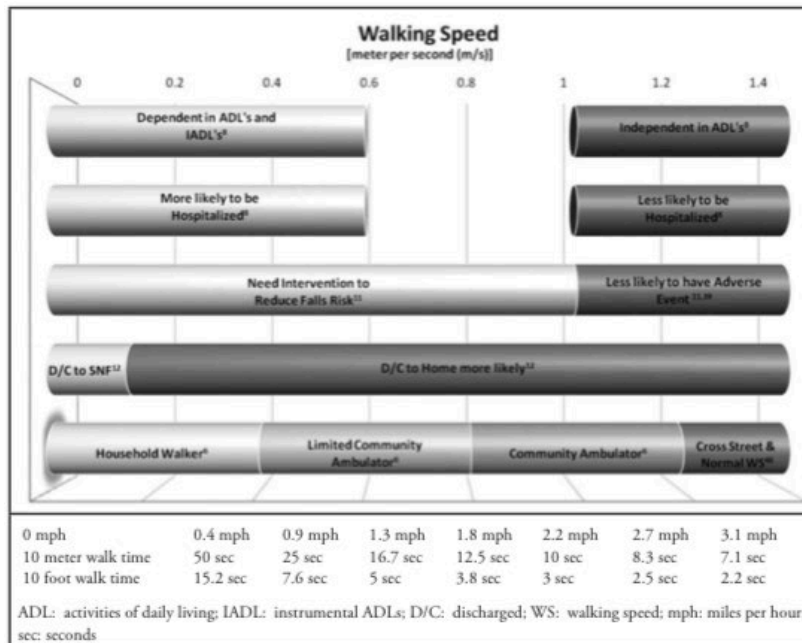
¹² Ada, Louise et al. “Improving community ambulation after stroke: the AMBULATE trial.” *BMC Neurology*. Vol. 9, no. 8, Feb. 2009.

¹³ van de Port, Ingrid G., Gert Kwakkel, and Eline Lindeman. “Community Ambulation in Patients with Chronic Stroke: How is it Related to Gait Speed?” *Journal of Rehabilitation Medicine*. 2008.

¹⁴ Durcan, Sarah. “An Investigation Of The Factors Associated With Community Ambulation In Chronic Stroke.” *Royal College of Surgeons in Ireland*. 2014.

¹⁵ Fritz, Stacy and Michelle Lusardi. “White Paper: ‘Walking Speed: the Sixth Vital Sign.’” *Journal of Geriatric Physical Therapy*. Vol. 32. 2009.

Figure 2: Walking Speed Correlates¹⁵



Neurologic Music Therapy (NMT) is often prescribed to address the mobility impairments caused by neurologic injuries and diseases and has been shown to leverage neuroplasticity (i.e., the rewiring of connections between different regions of the brain) by using rhythmic cueing. These interventions have been proven to couple the auditory and motor regions of the brain, which, over time, can lead to the permanent strengthening of a previously damaged motor region.

Despite the many benefits of NMT, the following shortcomings make it unscalable and thus, unusable as a solution for the wide-spread community with walking defects:

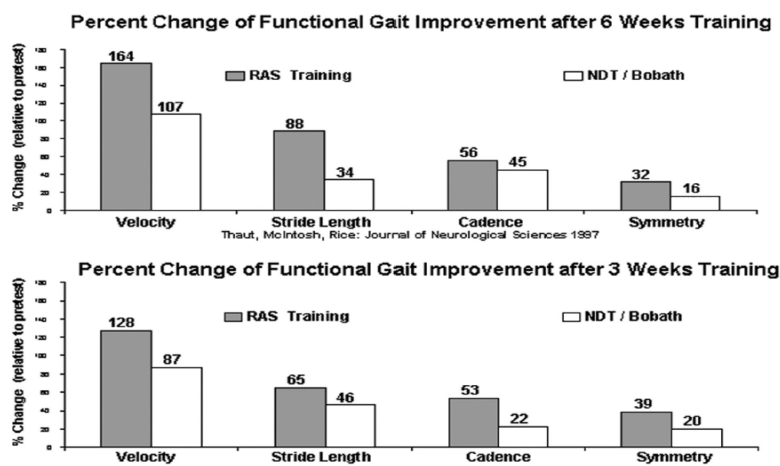
1. NMT is expensive
2. NMT is inaccessible to many who have trouble traveling to a clinic
3. There are too few NMT practitioners to serve all those who could benefit from these therapies (only 1,500 therapists in the world have NMT certification)

Based on the stroke guidelines and physician demand, there is an unmet need to improve walking deficits in the chronic stroke population. It has been shown that Rhythmic Auditory Stimulation (RAS), a term for the neurologic music therapy (NMT), makes an impact in this population and it is known that patients want solutions to this problem, however they don't have the means or the options.

RAS has been researched in the clinic in over 50 peer-reviewed studies. One study revealed that a group of post-stroke patients who were treated with RAS had better clinical outcomes than another group of

post-stroke patients who were treated with conventional physical therapy techniques.¹⁶ In this study, 43 stroke patients were treated with RAS and 35 were treated with a type of physical therapy called NDT/Bobath measured at 3 weeks and 6 weeks. A common rehabilitation goal for patients with post-stroke walking deficits is to improve walking speed while maintaining gait symmetry, which is a measure of balance. Speed, a composite of cadence (rate) and stride length (distance), is considered to be an indicator of walking ability¹⁵. During this study, the RAS group showed greater improvements in stride length, symmetry, cadence, and velocity at both 3 weeks and 6 weeks. These results are displayed in Figure 3 below. Randomized Controlled Trials have also demonstrated improved walking in other neurological conditions such as, Multiple Sclerosis¹⁷, Cerebral Palsy¹⁸, and Parkinson's Disease¹⁹.

Figure 3: Stroke Rehab Results Showing Improvement of RAS over a Physical Therapy technique¹⁶



The *Stride Plus* device, and its predecessor, the *Stride* device, are inspired by the success of the clinical application of NMT and a need for a parallel, digital option to improve walking rehabilitation across patient populations who have suffered from a neurological injury or disease and do not have access to the financing or to the top hospitals to undergo long-term NMT.

The MedRhythms *Stride Plus* is intended to not only assist in walking rehabilitation, but to achieve clinically meaningful outcomes in the chronic stroke population by increasing walking speed and converting individuals from limited community ambulators to community ambulators. This conversion of increasing walking speed is a clinically relevant outcome for the chronic stroke population, with a potential to reduce co-morbidities and a decline in overall health status caused by limited mobility.

¹⁶ Thaut, Michael, G.C. McIntosh, and R.R. Rice. "Rhythmic facilitation of gait training in hemiparetic stroke rehabilitation." *Journal of the Neurological Sciences*. Vol. 151, no. 2, Oct. 1997.

¹⁷ Conklyn, D. et al. "A home-based walking program using rhythmic auditory stimulation improves gait performance in patients with multiple sclerosis: a pilot study." *Neurorehabilitation and Neural Repair*. Vol. 24, no. 9, Nov. 2010.

¹⁸ Kim, S. et al. "Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls." *Journal of the Neurological Sciences*. Vol. 316, no. 1-2, May 15, 2012.

¹⁹ Bukowska, Anna A. et al. "Neurologic Music Therapy Training for Mobility and Stability Rehabilitation with Parkinson's Disease – A Pilot Study." *Frontiers in Human Neuroscience*. Jan. 26, 2016.

2 STUDY RISK

The investigational device does not meet the criteria of significant risk device as defined in 21 CFR 812.3(m), because the intended use and technological basis for *Stride Plus* does not meet the following criteria (paraphrased):

1. intended as an implant
2. purported or represented for use in supporting or sustaining human life
3. is for use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health, or
4. otherwise represents a potential for serious risk to health, safety or welfare of the subject.

Therefore, this study is designed to meet the abbreviated requirements of the Investigational Device Exemption regulation, 21 CFR 812.2(b)(1).

3 STUDY OBJECTIVES

2.1 Primary

The purpose of this clinical study is to demonstrate that after five weeks of training at three times per week with *Stride Plus*, participants representing limited community ambulators in the chronic stroke population will on average have increased their walking speed more than the active control group as measured by the 10 Meter Walk test. Additionally, the gait speed increase will be greater than the MCID of .15m/s.^{1,2}

2.2 Secondary

1. To demonstrate that after five weeks of training with *Stride Plus*, a larger proportion of participants in the intervention group will become community ambulators compared to the active control group.
 - a. Additionally, the proportion of participants who achieve a minimum 0.15 m/s change in gait speed *and* convert to community ambulator status will be greater in the *Stride Plus* group.
2. To show that the changes in Cadence, Stride Length, Temporal Symmetry, and Spatial Symmetry as measured by an instrumented walkway system at the completion of study participation are improved with *Stride Plus*.
 - a. There will be a positive correlation among these measures with those from the sensors of the *Stride Plus*.
 - b. No relationship will be seen on a Bland-Altman plot.
3. Quality life and self-perceived disability, as measured at the closing visit will have greater improvement in the *Stride Plus* group.
4. There will be no significant differences in safety or adverse outcomes between groups.

3 INVESTIGATIONAL DEVICE DESCRIPTION

The MedRhythms *Stride Plus* includes a patient application and sensors with commercially available headphones and smartphones. The *Stride Plus* is a device intended to improve gait metrics in the chronic stroke populations, with the goal of converting limited ambulators to community ambulators, by improving walking speed. It is also intended to track patient progress, and facilitate communication between patients, caregivers and clinicians. This technology uses Rhythmic Auditory Stimulation - embedded audio cues to facilitate improvements in walking speed. When using the system, patients walk with sensors that are attached to their shoes and collect gait parameters, including the following measurements: speed, stride length, symmetry (temporal and spatial), and cadence. When marketed, clinicians pre-program the device with the patients' rehabilitation goals, and the algorithm uses these endpoints and feedback from the sensors to inform changes made to the audio cues. These cues, which are embedded in time-shifted music, are delivered back to the users who aim to walk to the beat.

Research shows that walking to an external rhythmic stimulus globally engages the brain, coupling the auditory and motor regions. For stroke survivors with damage to the motor system, this dual engagement has the effect of establishing new neural connections to the motor region. Furthermore, this has the potential to make walking certain distances, which may ordinarily be onerous or impossible tasks, achievable for these individuals. As a result of neuroplasticity, repeating these audio-cueing exercises on a consistent basis can change one's brain composition, allowing walking improvements made with the device to manifest without the engagement of the intervention.

The MedRhythms *Stride Plus* device supplied as part of this protocol is **For Investigational Use Only**. The performance characteristics of the test have not been established. ***Study Subjects will be blinded to the results of the intervention (10-meter walk test). No results will be provided to the Study Subject at any time during participation in the trial.***

4 STUDY LOCATIONS

The study will be performed at a minimum of three (3) rehabilitation centers, hospitals or academic facilities under the supervision of study staff.

The applicable Institutional Review Board (IRB) for each participating site will review and approve the study protocol and informed consent documents prior to enrolling Subjects into this study. The total study duration is expected to be approximately six (6) months, with Subject enrollment targeted to begin mid-2019.

5 STUDY DESIGN

This study will be a multi-site, prospective, randomized controlled clinical study. The study will be performed at a minimum of three (3) rehabilitation centers, hospitals, or academic facilities under the

supervision of study staff. Each site will randomize participants at their location to cohorts using block randomization with randomly selected block sizes.

Approximately eighty Subjects (n=78) will be prospectively enrolled at a minimum of three (3) sites. Each site will target enrollment of 26 Subjects. Additional Subjects may be enrolled after authorization from the Sponsor.

Target Age:

Patients 50 years of age and older are eligible to participate (see Inclusion Criteria below). This target age was chosen in order to minimize potential bias by recruitment of younger stroke patients, shown to have better functional recoveries.²⁰

Race/Ethnicity:

All races and ethnicities are eligible to be enrolled.

Education Level:

All educational levels will be enrolled, e.g., no high school diploma, those with a GED or high school diploma, those with some college, those with a bachelor's degree and those with advanced degrees.

Geographic Diversity:

Enrollment is expected to achieve a full representation of geographic diversity in the United States (urban, suburban, rural) through a multi-site approach.

The Institutional Review Board (IRB) for each participating site must review and approve the study protocol and informed consent documents prior to enrolling Subjects into this study.

All interested, potential subjects will participate in the following study phase:

- 1) Screening: A study visit intended for execution of the informed consent form and collection of baseline data for eligibility

Individuals who qualify for enrollment per the inclusion/exclusion criteria will be notified and participate in the following study phases:

- 2) Enrollment: Confirmation of eligibility and randomization (no study visit required). Upon enrollment, patients will be randomized into one of two cohorts:

Cohort A: *Stride Plus* Intervention Arm

Cohort B: Active Walking Intervention Arm

All Study Subject's will be provided a schedule of intervention visits at this time.

- 3) Intervention: A series of fifteen (15) study visits intended to collect data toward study objectives

²⁰ Putaala, J., MD. (2017). *Defining Young Stroke*. Manuscript. Retrieved from <http://youngstroke.org/wp-content/uploads/2017/04/DefiningYoungStroke.pdf>

- 4) Post-Intervention: A single study visit intended to collect post-intervention data to measure change from baseline.

Cohort A: Stride Plus, is the Intervention Arm and will use the *Stride Plus*, headphones and sensors for 30 minutes at a time, 3 times a week, for 5 weeks and perform the 10-meter walk tests. Each session will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions.

Cohort B: Control Group, is the active control arm and will walk 30 minutes at a time with the *Stride Plus* sensors only, 3 times a week, for 5 weeks and perform the 10-meter walk tests. Each session will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. No mobile devices, music players or headphones will be used. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions.

The 10-meter walk test will be conducted twice per session, once at the beginning and once at the end. Physiological measurements will be taken at each study visit and abide by the Institution's standard operating procedures to ensure safety of the participants. Biomechanical, cognitive and stroke specific Quality of Life (ss-QoL) measurements will be taken only at the screening and post-intervention phase. Photos or videos may be taken as Study Subjects complete research activities to allow offline analyses by investigators who were not at study visits and for use in publications or presentations. All video and photographic data that is taken will not contain any Study Subject names and will be stored on a password protected server with access limited to study staff. Every attempt will be made to avoid capturing participants' faces.

Each Subject's data will be recorded on source documentation and transcribed into electronic Case Report Forms (CRFs) within the web-based Electronic Data Capture (EDC) system set-up by MedRhythms.

This study will be listed on clinical trials.gov. Therefore, results will be published per FDA requirements.

5.1 Use of Data

As the investigational MedRhythms *Stride Plus* is not FDA cleared for sale in the US, it is **For Investigational Use Only**. The performance characteristics of this test have not been established. Study Subjects will be blinded to the results of the intervention (10-meter walk test). No results will be provided to the Study Subject at any time during participation in the trial.

Data collected from the sensors used in both cohorts may be used for future product development, product clearance/registration and/or product improvement.

5.2 Study Duration

Each Subject is required to complete seventeen (17) visits and ideally will occur over six (6) weeks. Rescheduling needs may increase the total number of weeks of involvement. The duration of Subject involvement at each visit is contingent on the visit purpose. However, it is expected that the screening (visit 1) and closing visit (visit 17) will take up to three (3) hours and the training visits (visits 2 – 16) will take approximately ninety (90) minutes. No follow-up or subsequent Subject involvement is required once the closing visit is complete.

6 STUDY ENDPOINTS

The primary study endpoint will be the mean increase in gait speed (m/s) and mean percent increase in gait speed as determined by a 10-Meter Walk Test after five weeks of training and compared between groups.

7 STUDY MATERIALS

7.1 Sponsor Provided

The following materials will be provided by MedRhythms to the Investigator:

1. Access to *Stride Plus* patient application.
2. Mobile Devices.
3. GaitUp Sensors.
4. Headphones.
5. If needed, vital monitors.
6. If needed, electronic storage devices, e.g., thumb drives.
7. Regulatory Binder containing the following:
 - EDC system instructions for access to and usage of electronic Case Report Forms
 - Training documents on study logistics, e.g., SIV slide presentation and case report form instructions
 - Written *Stride Plus* user instructions
 - Cognitive assessment materials
 - Questionnaires; and

- Study logs, (e.g., device inventory log, delegation of authority, screening and enrollment logs, monitoring visit log, protocol deviation log, adverse events etc.).

7.2 Investigator Provided

The following materials will be provided by the Investigator to MedRhythms:

1. Documentation of properly obtained Institutional Review Board (IRB) approval (on IRB letterhead) from the central or local IRB containing the following:
 - IRB classification of protocol;
 - Date of IRB approval;
 - Next continuing review date; and
 - IRB chairperson/administrator signature.
2. IRB approved Consent and Authorization Form.
3. Curriculum Vitae of Principal Investigator signed and dated.
4. List of all personnel who will have significant involvement in the research study, including practicing license (i.e., MD, RN) and role in the study.
5. Financial Disclosure Form from the Principal Investigator (and Sub-Principal Investigator, if applicable) directly involved in the evaluation of research Subjects in this study.
6. Documentation of training on basic human research Subject's protection for the Principal Investigator and all personnel who will be administering informed consent.
7. Signed and dated Investigator Acknowledgement (see Appendix A of this protocol).
8. If appropriate, a copy of relevant protocols used.
9. Completed CRFs for each Subject enrolled in the study.
10. Completed, signed and dated study logs.
11. All sensors, mobile devices, headphones and, if applicable, vital monitors or other measuring devices provided by the Sponsor for return to MedRhythms at the conclusion of the study.

8 PROSPECTIVE STUDY SUBJECTS

8.1 Number of Subjects

Approximately eighty Subjects (n=78) meeting the study inclusion/exclusion criteria will be prospectively enrolled.

8.2 Inclusion/Exclusion Criteria

To be enrolled in the study, each Subject must meet all of the following inclusion criteria and none of the following exclusion criteria:

8.2.1 Inclusion Criteria

1. 50 years of age and older
2. Equal to or greater than six months post-stroke, as determined by past medical history review
3. Currently able to walk at a speed greater or equal to 0.5m/s, but less than 0.8m/s, as determined by a 10-meter walk test (the average of three trials) for comfortable walking speed without using assistive devices²¹.
4. Demonstrates some level of asymmetry in gait
5. Able and willing to consent with proposed study schema (verbal commitment), including consent to participate in communication with the treating clinician (as needed) during the study period
6. Score ≤ 1 on question 1b and a 0 on question 1c on the NIH Stroke Scale
7. Able to safely participate in protocol-defined walking therapy sessions of 30 minute duration as determined by the Investigator.

8.2.2 Exclusion Criteria

1. Subject is currently enrolled in study to evaluate an investigational drug.
2. Subject has already participated in this study.
3. Subject unable or unwilling to provide informed consent.
4. Subject is unable to participate in protocol-defined walking therapy sessions of 30-minute duration without the use of assistive devices as determined by Subject and Principal Investigator.
5. Subject is considered a community ambulator (walking speed ≥ 0.8 m/s) when not using an assistive device²¹ as determined by a 10-meter walk test for comfortable walking speed (the average of three trials).
6. Has a known history of neurologic (excluding stroke) injury, as determined by past medical history review
7. Has had more than 2 falls in the previous month, as determined by patient self-report
8. Is enrolled in another walking rehabilitation intervention (e.g., physical therapy)
9. Has an external lower limb prosthetic ("artificial limb"), as determined by patient self-report

²¹ Assistive devices are defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted.

10. Has a hearing impairment, as determined by past medical history review
11. Had orthopedic surgery in the last year, as determined by past medical history review
12. Has severe aphasia and/or a speech/language disorder, limiting ability to express needs and comprehend instructions, as determined by past medical history review
13. Has co-morbidities that prevent participation in exercise, as determined by past medical history review (for example: musculoskeletal, cardiovascular, pulmonary and neurological – other than stroke)
14. Vulnerable populations as deemed inappropriate for study by site Principal Investigator.

8.3 Subject Discontinuation

Subjects may discontinue their participation in the study at any time. A Subject may be withdrawn from the study at any time at the discretion of the Investigator.

8.4 Subject Withdrawal, Drop Out and Replacement

Subjects who are withdrawn or drop out prior to completing all fifteen (15) training visits and/or a closing visit will still have data that was collected up until the withdrawal/drop out eligible for analysis (see section 13, Statistical Considerations). These Subjects will be analyzed in an Intent-To-Treat analysis.

Subjects who are withdrawn or drop out from the study may be replaced at the Sponsor's discretion in order to meet the primary study endpoint.

9 PROSPECTIVE STUDY PROCEDURES

9.1 Recruitment

Recruitment may occur via email (using IRB-approved language), IRB-approved flyers, promotional videos, or word of mouth through the following:

- a. Clinicians at clinics, centers, and institutions with whom the investigators have developed collaborating relationships may approach patients who they believe may be interested in participating in the study to inform them about the study. These clinicians will not be actively recruiting for the study.
 - i. If these patients are interested, they will be provided with a research flyer which they can use to initiate contact with study staff.
- b. Clinical research programs at the study site locations keep the contact information of patients who have had a diagnosed stroke and are interested in participating in research.
 - i. Potential Study Subjects from these registries will be contacted via email or phone and asked if they wish to learn more about the study. If they are interested, they will be provided with a flyer that they can use to initiate contact with study staff.

- c. Clinicians at rehabilitation hospitals and clinics at the study site locations will be provided with IRB-approved recruitment materials that they can make available to their patients.
 - i. Patients that are interested can then use the information in these materials to initiate contact with study staff.
- d. Study investigators may be invited to speak about the study to relevant organizations, including recreational/social programs, support groups, etc. Study flyers will be left at or provided to these locations for distribution.
 - i. Individuals that are interested can then use the information on these flyers to initiate contact with study staff.
- e. Information about the study may also be distributed via the following methods with prior approval from site staff/managers:
 - i. At local stroke support group meetings and in university or hospital buildings
 - ii. Relevant programs serving persons with disabilities (e.g. stroke survivor programs, sports or recreational programs)
 - iii. Relevant newsletters serving people with disabilities
 - iv. Relevant buildings around study locations, at local businesses (e.g. coffee/sandwich shops), at local health or fitness centers
 - v. Relevant websites such as Craigslist or print papers, social media sites or groups (e.g. stroke survivor Facebook groups)

Study Subjects will be identified for enrollment, provided with a brief description of the study (flyer) and if interested, will contact study staff for a ten-minute phone call. During this first conversation, the goals of the study will be clearly described, and the potential Study Subjects will be asked questions to ascertain whether they preliminarily meet the study's inclusion/exclusion criteria. If they remain preliminarily eligible and interested, they will be invited to participate in the screening study visit.

9.2 Screening Visit (Visit 1, Day -30 to 0)

During the initial screening visit (up to 3 hours), the study's purpose and its potential risks and benefits will be explained to potential study Subjects. Subjects will formally enter the screening phase of the study only after providing their written informed consent. After Subjects provide their written informed consent, they will be assigned a unique screening identifier by study staff. The Principal Investigator (PI) at each site will maintain a master log that will correlate each screening ID to the Subject's name. This log will remain at the study site and will be confidential.

The following is a list of activities and forms that will be conducted during the screening phase, unless otherwise noted as optional and/or dependent on institutional policies and procedures:

- a. *Demographic and Medical History*: a study staff member will collect the following demographic information: Age, Gender, Race, Ethnicity and Education Level. Study staff will also collect all significant past and/or concomitant medical conditions, disease, or surgeries and is to identify

the body system, relevant medical term, start date and, if applicable, stop date. Study staff may collect the information by interviewing the Study Subject and/or reviewing the past medical history in the Subject's medical record.

- b. *Cognitive Screening:* a study staff member will perform questions 1b and 1c from the NIH Stroke Scale. No other portions of the scale need to be performed for the purposes of this study.
- c. *Baseline Walking Measurements:* A trained member of the study staff will conduct the 10-meter Walk Test and performed according to their institution's standard procedures. However, for the purposes of this study, three (3) trials each of both comfortable and fast walking speed must be performed with the use of a handheld stopwatch. Study Subjects who use assistive devices will be evaluated by the Investigator for ability to perform the 10-meter walk test without the use of their devices. For the purposes of this study, an assistive device is defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted. Study Subject's will **not** be asked to focus on particular aspects of their walking and feedback on these aspects **will not** be provided through visual, auditory, or tactile cues. **To be eligible for enrollment, the results of the 10MWT must be within seven (7) days of planned enrollment into the study.** Therefore, this procedure may be repeated only if the results of the original screening procedure are > 7 days old.

In addition, the Investigator will evaluate the Subject's ability to perform the protocol-defined walking therapy of 30-minute duration without assistive devices based on medical history and/or any other walking measurements deemed appropriate. The Investigator's evaluation will be documented in the Subject's research file.

- d. *Quality of Life:* Subjects will be self-administered the stroke-specific Quality of Life Scale. For the purposes of this study, a proxy will not be allowed. However, Subject's may use the assistance of a caregiver, friend or family member, or a member of the study staff to write their answers. Study staff will be responsible for reviewing the Subject's responses for completeness and legibility.
- e. *Self-Perceived Disability:* Subjects will be self-administered the Stroke Impact Scale. For the purposes of this study, a proxy will not be allowed. However, Subject's may use the assistance of a caregiver, friend or family member, or a member of the study staff to write their answers. Study staff will be responsible for reviewing the Subject's responses for completeness and legibility.
- f. *Physiological Measurements:* If necessary for ensuring a Subject's ability to safely participate in walking therapy (e.g., required per institutional policy), a trained member of the study staff may collect physiological measurements, e.g., heart rate, blood pressure, respiration rate, following

the site's standard operating procedures. Data will not be transcribed into the CRF, but the Investigator's evaluation will be documented in the Subject's research file, including any medical clearance as necessary. The validity period of the measures will be per institutional policy/investigator discretion and should be repeated as necessary to support the evaluation of the Subject's eligibility.

- g. *Biomechanics*: Biomechanical data will be collected using the institution's validated instrumented walkway system and performed according to their standard procedures. However, for the purposes of this study, three (3) trials of self-selected *comfortable* walking speed must be performed and the results averaged for cadence, stride length, temporal symmetry and spatial symmetry. If the institution will be using a GAITRite® walkway, the 10MWT cannot be performed simultaneously. Study Subjects who use assistive devices will be evaluated by the Investigator without the use of their devices. For the purposes of this study, an assistive device is defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted. Study Subject's will **not** be asked to focus on particular aspects of their walking and feedback on these aspects **will not** be provided through visual, auditory, or tactile cues. **Biomechanical results must be within seven (7) days of planned enrollment into the study as results will be used to support secondary objectives.** Therefore, this procedure may be repeated only if the results of the original screening procedure are > 7 days old.
- h. *Photo/Video Data*: Photos or videos may be taken as Study Subjects complete research activities to allow offline analyses by investigators who were not at study visits and for use in publications or presentations. Because the focus of this study is on walking, every attempt should be made to avoid capturing participants' faces. All video and photographic data that is taken will not contain any Study Subject names and will be stored on a password protected server with access limited to study staff.

9.3 Enrollment (Day 0)

Individuals that do not qualify for enrollment per the inclusion/exclusion criteria or otherwise do not meet the criteria by the end of thirty (30) days from consent are **not** eligible to participate and will be immediately notified. These individuals will be considered Screen Failures. These individuals may be screened again in the future, if feasible and at investigator discretion.

Individuals who submit answers that do qualify them for enrollment per the inclusion/exclusion criteria are eligible to participate and will be formally enrolled (no study visit required). Upon enrollment, patients will be randomized into one of two cohorts:

9.3.1 Cohort A: *Stride Plus* Intervention Arm

The *Stride Plus*, headphones and sensors will be used by study Subjects for 30 minutes at a time, 3 times a week, for 5 weeks and perform the 10-meter walk tests. Each session

will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions.

9.3.2 Cohort B: Active Walking Intervention Arm

Subjects will participate in active walking for 30 minutes at a time with the *Stride Plus* sensors only, 3 times a week, for 5 weeks and perform the 10-meter walk tests. Each session will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. No mobile devices, music players or headphones will be used. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions.

9.4 Visit Schedule

All Study Subjects will be contacted to establish a schedule of intervention visits that should begin within one (1) week of enrollment. The training phase of the study requires a series of fifteen (15) study visits intended to collect data towards study objectives. Training visits will be scheduled for three (3) times a calendar week for five (5) weeks and must commence on or within 7 days of enrollment & randomization. No more than three (3) visits can be scheduled during a calendar week.

9.4.1 Rescheduling

In circumstances where the Subject must miss a visit, the visit should be rescheduled within the same calendar week.

a. Training Visits 1 - 6

Subjects must complete the first six (6) consecutive visits to remain eligible for continued participation in the study. Subjects who do not complete the first six (6) consecutive visits will be asked to restart the study training visit schedule. See section 9.4.1.c for restart requirements. Subjects unwilling to restart will be withdrawn from the study and are not eligible to re-enroll.

b. Training Visits 7 – 15

Subjects who have completed the first six (6) consecutive visits and cannot reschedule a missed visit within the same calendar week, must have the missed visit scheduled after completing the planned 5th week. Please note, when rescheduling visits past the 5th week, no more than 3 visits can be scheduled during a calendar week.

Subjects who miss more than three (3) consecutive visits (regardless of the calendar week), will be asked to restart the study training visit schedule. See section 9.4.1.c for

restart requirements. Subjects unwilling to restart will be withdrawn from the study and are not eligible to re-enroll.

Subjects who resume training after a missed visit(s) must complete a total of three (3) consecutive training visits (regardless of calendar week) to be eligible to miss another visit. Subjects will not be allowed to miss a visit, attend the next 1-2 training visits and then miss another visit that cannot be made up within the same calendar week. Otherwise, Subjects will be asked to restart the study training visit schedule. See section 9.4.1.c for restart requirements. Subjects unwilling to restart will be withdrawn from the study and are not eligible to re-enroll.

c. Restart Requirements

Subjects who require and are willing to restart the study training visit schedule due to missed visit parameters defined above, must complete a washout period equivalent to the length of time (in weeks) of their prior training visit participation. An additional 1-2 weeks during the washout period may be necessary to accommodate scheduling needs of the study site and Subject or in the best interest of the Subject's health status based on Investigator discretion. A new baseline measurement of gait speed must be obtained within the acceptable gait speed parameters defined in the inclusion criteria for the subject to be able restart at the conclusion of their washout period. Subjects whose gait speeds fall outside of the defined parameters will be withdrawn from the study and are not eligible to re-enroll.

9.5 Training Visits (Visit 2-16, Weeks 1 -5)

Subjects will perform the 10-meter walk test (10MWT) twice at each session (once at the beginning and once at the end). The 10MWT is to be performed according to their institution's standard procedures. However, for the purposes of this study, three (3) trials each of both comfortable and fast walking speed must be performed with the use of a handheld stopwatch. Study Subjects who use assistive devices will must perform the 10MWT without the use of their devices. For the purposes of this study, an assistive device is defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted. Study Subject's will **not** be asked to focus on particular aspects of their walking and feedback on these aspects **will not** be provided through visual, auditory, or tactile cues.

All Study Subject's will be provided with all necessary equipment (pre set-up). Subjects will conduct 30 minutes of walking therapy at the participant's self-selected pace **without the use of assistive devices**. Study staff will provide appropriate oversight of the Subject during walking therapy to ensure safety. The use of an overhead harness system is prohibited in this study. Study staff will provide minimal instructions to the Subject before training begins, not during. Participants may choose to take breaks as needed, or when investigators believe that a rest break is necessary. If technical or medical issues arise,

the training session should be terminated to allow for adequate resolution. A new training session may be started only if fifteen (15) minutes or less of the prior session was completed and both the Subject and Investigator agree that the Subject is able to complete a new 30-minute walking practice.

Each session will be performed in a space (e.g., track or hallway) that limits the amount of stops and/or pivot turns in order to optimize velocity (e.g., a hallway 100 feet in length) and under the supervision of study staff. In addition, the space used for training sessions must not have any discernible music playing and remain limited in other potential audible distractions.

During these visits, clinical and physiological data will be measured concurrently as described below:

- a. *Photo/Video data:* Photos or videos may be taken as participants complete research activities to allow offline analyses by investigators who were not at study visits and for use in publications or presentations. Because the focus of this study is on walking, every attempt should be made to avoid capturing participants' faces. All video and photographic data that is taken will not contain any Study Subject names and will be stored on a password protected server with access limited to study staff.
- b. *Monitoring Physiological Parameters:* A trained member of the study staff will collect physiological measurements, e.g., heart rate, blood pressure, respiration rate, according to the site's standard procedures and at investigator discretion to ensure safety of the Study Subject.

If a Study Subject's vital measurements fall outside of the Institution's acceptable parameters, the study staff and Investigator are permitted to pause or terminate the training session. The decision as to how to proceed will be made in collaboration with the study Investigator and the Subject. If the session was terminated, a new training session may be started only if fifteen (15) minutes or less of the prior session was completed and both the Subject and Investigator agree that the Subject is able to complete a new 30-minute walking practice.

The Investigator will be responsible for determining any appropriate medical follow up that may be needed. Physiological measurement data will not be transcribed into the CRF; however, the data must be maintained in the Subject's research file and relevant data described in CRFs pertaining to adverse event evaluation and reporting, if necessary.

9.5.1 *Stride Plus* Procedure

Study staff will be required to follow the Instructions For Use (IFU) provided by MedRhythms. The IFU will detail all procedures required for both Cohorts A and B. All study staff will be trained in utilizing the *Stride Plus*. Mobile devices that have the MedRhythms *Stride Plus* application installed will be provided for use during study visits. Subjects will not interact with the mobile device; therefore, they will not be required to establish a username or password. Study staff will be responsible for setting up the

Stride Plus application (i.e., adding the Subject profile and maintaining login) prior to Subject use at each training visit. No personally identifiable patient information will be recorded or stored in the *Stride Plus* application.

9.6 Closing Visit (Visit 17 or at Withdrawal)

During the closing visit (up to 3 hours), which will occur 1 - 4 days after the last training visit, the activities listed below will be performed. If possible, Subjects who withdraw from the study early may complete the following visit activities either at the last training visit or within four (4) days of the last training visit.

- a. *Medical History Review:* a study staff member will review the Study Subject's medical history information collected throughout the course of participation in the study to identify any changes, e.g., adverse events such as falls and any significant changes in health status and diagnoses.
- b. *Closing Walking Measurements:* A trained member of the study staff will conduct the 10-meter Walk Test and is to be performed according to their institution's standard procedures. However, for the purposes of this study, three (3) trials each of both comfortable and fast walking speed must be performed with the use of a handheld stopwatch. Study Subjects who use assistive devices must perform the 10-meter walk test without the use of their devices. For the purposes of this study, an assistive device is defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted. Study Subject's will **not** be asked to focus on particular aspects of their walking and feedback on these aspects **will not** be provided through visual, auditory, or tactile cues.
- c. *Quality of Life:* Subjects will be self-administered the stroke-specific Quality of Life Scale. For the purposes of this study, a proxy will not be allowed. However, Subject's may use the assistance of a caregiver, friend or family member, or a member of the study staff to write their answers. Study staff will be responsible for reviewing the Subject's responses for completeness and legibility.
- d. *Self-Perceived Disability:* Subjects will be self-administered the Stroke Impact Scale. For the purposes of this study, a proxy will not be allowed. However, Subject's may use the assistance of a caregiver, friend or family member, or a member of the study staff to write their answers. Study staff will be responsible for reviewing the Subject's responses for completeness and legibility.
- e. *Physiological Measurements:* If necessary (e.g., required per institutional policy), a trained member of the study staff will collect physiological measurements, e.g., heart rate, blood pressure, respiration rate, following the site's standard operating procedures. Data will not be transcribed into the CRF; however, the data must be maintained in the Subject's research file

and relevant data described in CRFs pertaining to adverse event evaluation and reporting, if necessary.

- f. *Biomechanics*: Biomechanical data will be collected using the institution's validated instrumented walking system and performed according to their standard procedures. However, for the purposes of this study, three (3) trials of self-selected *comfortable* walking speed must be performed and the results averaged for cadence, stride length, temporal symmetry and spatial symmetry. If the institution will be using a GAITRite® walkway, the 10MWT cannot be performed simultaneously. Study Subjects who use assistive devices will be evaluated by the Investigator without the use of their devices. For the purposes of this study, an assistive device is defined as a cane, crutch, walker, and/or external functional neuromuscular stimulator (FES) device; however, a lower limb orthosis (brace) is permitted. Study Subject's will **not** be asked to focus on particular aspects of their walking and feedback on these aspects **will not** be provided through visual, auditory, or tactile cues.
- g. *Photo/Video Data*: Photos or videos may be taken as Study Subjects complete research activities to allow offline analyses by investigators who were not at study visits and for use in publications or presentations. Because the focus of this study is on walking, we will make every attempt possible to avoid capturing participants' faces.

9.7 Schedule of Assessments

	Screening	Enrollment	Training Visit 1	Training Visits 2 – 15	Rescheduled Visits*	Closing
Timepoint	(-30 days** to 0)	(Day 0)	(Day 1+7)	(Weeks 1-5)	(Week 6 – 7)	(≤ 4 days of last training visit)
Informed Consent	x					
Demographic & Medical Hx	x					
1b & 1c – NIH Stroke Scale	x					
Walking Measurement (10 MWT)	x**		x [†]	x	x	x
ss-QoL	x					x
Stroke Impact Scale	x					x
Physiological Measurements***	x		x	x	x	x
Biomechanics	x**					x
Inclusion/Exclusion Criteria Evaluation		x				
Randomization		x				
Visit Scheduling		x				
Cohort A: Stride Plus Device Use			x	x	x	
Cohort B: Active Walking			x	x	x	
Adverse Events			x	x	x	x
Medical Hx Short Form						x

* Training visits may be rescheduled in accordance with the criteria in section 9.4, Visit Schedule.

** The results of the 10MWT and biomechanical data are the only screening measures that must be within seven (7) days of planned enrollment into the study. Therefore, these procedures may be repeated only if the results of the original screening procedures are > 7 days old.

*** Collected, if necessary, for ensuring a Subject's safety in walking therapy, e.g., required per institutional policy (see sections 9.2.f, 9.5.b and 9.6.e).

[†] For Subjects who restart training visits (see section 9.4), the new baseline walking speed must be within the parameters defined in the inclusion/exclusion criteria.

10 CASE REPORT FORMS

The information required for completion of the CRF is as follows:

1. Subject Information
2. Screening Visit Information
3. Training Visit Information (x 15)
4. Closing Visit Information
5. Comments (Enter Comments)
6. Adverse Events (Yes/No)
7. Principal Investigator Signature and Date

11 PROSPECTIVE SUBJECT INVOLVEMENT ENDPOINT/FOLLOW-UP

All Subjects who sign the Consent and Authorization Form and complete the seventeen (17) study visits have completed participation in this study. No direct Subject follow-up by study Investigators is planned for volunteer Subjects participating in this study.

12 SAFETY CONSIDERATIONS

12.1 Definitions of Adverse Events

An **Adverse Event (AE)** is any untoward or unfavorable physical or psychological occurrence in a Study Subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with participation in the research, whether or not considered related to participation in the research. The PI will be notified when any adverse event is identified.

A **Serious Adverse Event (SAE)** is any adverse event that results in any of the following outcomes:

- Results in death
- Is life-threatening (places the participant at immediate risk of death)
- Results in hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- May jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Unexpected Adverse Event is any adverse event occurring in one or more Study Subjects, the nature, severity, or frequency of which is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved protocol, any applicable investigator brochure, and the current

IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts, or

- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

It should be noted that adverse events that lead to hospitalization are considered SAEs. However, elective hospital admissions not in response to an adverse event are not SAEs.

Life-threatening means that the Subject was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred. This definition does not include a reaction, which in a more serious form might have caused death. Assessment of the cause of the event has no bearing on the assessment of the event's severity.

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

AE data collection commences when the Subject signs the informed consent form. AEs will be collected at each study visit. Data to be collected will include the description of the event, onset and resolution dates (or whether the event is ongoing), severity, management/treatment, outcome, and determination of the relationship to the device used. Adverse events (AE) will be considered to be **intervention-related** if, in the view of the investigator, the event was caused by or associated with the intervention. Deaths, organ failures and other complications related to the Subject's underlying conditions (including the disease or problem that caused the Subject to seek medical care) - should **not** be considered study-related adverse events. A pre-existing condition is one that is present prior to or at the start of the study and is to be reported in Subject's medical history. A pre-existing condition should be reported as an adverse event only if the frequency, intensity, or the character of the condition worsens during study participation.

If an AE is considered intervention-related, the categories will be further described as definitely, probably, or possibly-related using the following definitions:

- 1) *Definitely intervention-related*: Any event that is associated with the device by timing and physiology, and was caused or contributed to by the device.
- 2) *Probably intervention-related*: Any event that is associated with the device by timing and physiology, and there is a good chance that it may have been caused or contributed to by the device.

- 3) *Possibly intervention-related*: Any event that is associated with the device by timing and physiology, and there is a possibility that it may have been caused or contributed to by the device.

Severity of the AE will be coded as to the degree of severity as follows:

1. *Mild*: Awareness of the event but easily tolerated.
2. *Moderate*: Discomfort enough to cause interference with usual activity.
3. *Severe*: Inability to carry out usual activity (not necessarily the same as a Serious Adverse Event. Subjects may have a severe flu but not require hospitalization.)

The frequency of adverse events total and by severity will be compared between intervention groups using an equivalence trial framework.

12.2 Possible Risks & Benefits Associated with Study Procedures

12.2.1 Benefits

This project will facilitate the development and clinical translation of targeted gait interventions that can improve post stroke walking ability through specific action on the impairments most likely to be limiting mobility and participation after stroke, including the development of new technology that extends the abilities of clinicians.

12.2.2 Risks

There are some risks to participating in this study. We have categorized them below as *Possible*, *Less Likely*, and *Rare* risks. In summary, the expected risks include:

12.2.2.1 Possible risks:

- Fatigue
- Nausea
- Shortness of breath
- Muscle or joint soreness
- Minor muscle cramps
- Loss of balance or fall
- Skin redness/inflammation/chafing/hair pulling (from sensor tape)

Fatigue; Muscle or joint soreness – Depending on participants' level of disability, sessions will be mildly to moderately strenuous. The

participant may become fatigued, or experience joint soreness in their hip, knee, ankle or foot.

Fatigue; Nausea; Shortness of breath; Muscle cramps or muscle soreness – As with any exercise, there is the possibility that abnormal responses could occur. These include nausea, shortness of breath, fatigue, muscle cramps or soreness (lasting into subsequent days after testing).

Loss of balance or fall:

There is a risk of falling to the ground. Participants who typically wear an ankle brace may be asked to walk without the brace. When walking without the brace, the foot and ankle may not be as stable and there is an increased risk of ankle sprains during walking and falling.

Skin redness/inflammation/chafing/hair pulling (from sensor tape):

The double-sided medical grade tape used to place the instrumented walkway markers on the participant may cause some slight skin redness when taken off. This is a normal reaction and will disappear with time. Hair may also be pulled by the sensor tape.

12.2.2.2 Less Likely Risks:

- Muscle strain/tear
- Injury due to fall (ankle sprain, twisted knee, etc.)
- Abnormal physiological response to physical activity
- Irregular heart rate
- Fainting
- Bruising and bleeding

Muscle strain/tear; Injury due to fall:

Injuries such as muscle strains and tears are also possible due to exercise activities. Injuries due to falling are also possible.

Abnormal physiological response; Irregular heart rate; Fainting:

As with any exercise, there is the possibility that abnormal responses could occur. These abnormal responses include unexpected changes in blood pressure, irregular heart rate, fainting, or joint injury. This risk is increased in the post stroke population.

Bruising and bleeding:

Participants who are taking anticoagulants may be at increased risk for bruising and bleeding due to a fall.

12.2.2.3 Rare Risks:

- Heart problems
- Hospitalization
- Anxiety
- Heart attack
- Stroke
- Death

Heart and lung problems; Hospitalization:

As with any exercise, there is the possibility that abnormal responses could occur. Rare risks associated with exercise could include heart problems or hospitalization and in very rare cases, stroke and death. There is also a risk of pulmonary embolism.

Anxiety:

There also is a potential risk for Study Subjects to become anxious.

The PI and co-investigators have extensive experience with clinical research involving individuals poststroke. Many of the investigators are licensed physical therapists and most study staff and students have training in CPR and first aid. All the aforementioned risks will be mitigated through the following:

- Potential Study Subjects will be provided with the consent form and be provided ample time to read it and ask questions. The research team will address any concerns. Study Subjects will be told that participation in the study is completely voluntary and they have the right to withdraw from the study at any time.
- Adequate rest periods and water will be provided to optimize comfort and reduce fatigue.
- Total walking time per session will be limited to one hour.
- Trained investigators will monitor vital signs and check for symptoms of distress at each study visit. Any findings out of the ordinary will be reported to the participant's primary healthcare provider or emergency services should they require medical attention.

All participants are free to end testing or procedures that cause anxiety or discomfort at any time, this will not affect any remuneration or transportation they are entitled to. As with Adverse Events, frequency of side effects will be compared between groups using an equivalence trial framework.

12.3 Reporting Requirements

Any adverse events that occur during the study that the Investigator believes are **serious AND qualify as either an unanticipated adverse device effect OR are related to the investigational device** as defined above must be reported to MedRhythms within 24 hours to:

Danielle A. Briggeman
MedRhythms, Inc.
183 Middle Street, Suite 300
Portland, Maine 04101
(P) 207-956-2726

The IRB must also be informed in a timely manner. The Investigator will then submit a detailed written report to MedRhythms and the IRB no later than five (5) days after the Investigator discovers the event.

MedRhythms will be responsible for reporting any reportable serious, unexpected, device-related adverse events from this study to FDA and other applicable regulatory agencies.

13 STATISTICAL CONSIDERATIONS

13.1 Data Analysis

Data analysis as described in this section will be performed by a PhD level Statistician either in-house at MedRhythms, or as a paid consultant. All analyses will be performed twice, first as a Per protocol analysis (all data for participants who complete the study) and secondly as an Intent-to-treat analysis (all participants data included after being randomized). If the results of the two analyses differ, the Intent-to-treat results will be reported. Descriptive statistics will be reported for the entire sample and for each intervention arm using mean and standard deviation or frequencies and percentages for continuous and categorical variables, respectively. To ensure that the groups are equivalent from randomization t-tests and chi-square tests will be used to assess if potential covariates differ between groups. Significant covariates will be included in the analysis to reduce confounding by adjusting for them. Results will be reported as parameter estimates, with Confidence intervals, and effect sizes where appropriate. Alpha will be set to .05 for primary outcomes and .01 for secondary outcomes.²² All assumptions for all models will be assessed and remedied as appropriate.

Primary Endpoint: The two primary outcomes will be collected from performance data. The first is gait speed taken from the 10MWT and the second is percent change in gait speed, which is defined as

²² Please see section 13.2.1 for updated information.

$$GS_{\Delta per} = \frac{(GS_{\Delta})}{GS_s} \times 100,$$

where $GS_{\Delta} = GS_p - GS_s$ is change in Gait speed from screening visit, GS_s , to post-intervention, GS_p . These will be evaluated using General Linear Mixed Models (GLMMs). For gait speed a 2 x 2 GLMM will be performed, with individuals nested within sites. The interaction of group by time will be tested and if significant post-hoc comparisons will be performed comparing time within each group. The change over time for the *Stride Plus* group will also be compared to a null hypothesis value of .15 to see if the average change seen is beyond the MCID. The GLMM for GS_{Δ} is analogous to a two-sample t-test but allows for the nesting of individuals within sites.

Secondary Outcomes: Secondary outcomes include Community Ambulation status, defined as walking speed >.8m/s, measures from an instrumented walkway including- Cadence, Stride Length, Temporal Symmetry, and Spatial Symmetry, lastly self-reported measures of QoL and perceived disability. The Community Ambulation rates will be compared between groups using a chi-square test. A Mantel-Haenszel test will be used to see if Community Ambulation Stats along with changes in walking speed > .15 differ between intervention groups. Instrumented walkway and self-reported measures will be analyzed using the same model as that of Gait Speed.

Measures from the instrumented walkway will be correlated with those from the *Stride Plus*, using Pearson Correlations unless assumptions are not met in which case Spearman or Polychoric correlations will be used. Additionally, Bland-Altman plots will be used to assess agreement between them. The graph will be a scatterplot of the difference between the two paired measurements on the Y axis and plotted against the average of the two measurements on the X axis.

Model Justification: GLMMs will be used to test if the change in gait speed and percent change in gait speed over time differed between treatment conditions. The Mixed Model approach is more appropriate for several reasons. First, it will allow us to include study site as a random effect to adjust for potential variability seen due to site to site differences. Second, it is common in clinical trials to have missing data, as they allow for participants to drop-out and discontinue. GLMMs calculate estimates while accounting for missing data, which the classic ANOVA cannot. This offers a power advantage over ANOVAs that use listwise deletion or requires imputing data, such as the Last Observation Carried Forward, which can introduce bias. This method will allow us to get estimates for both the Per-protocol sample as well as the Intent-to-treat sample. Third, the GLMM procedure allows the direct specification of the residual covariance matrix, which negates the need to satisfy the restricting assumptions of homogeneity of covariance matrices and sphericity present in ANOVA. Lastly, GLMMs also enable the estimation of random intercepts and random slopes. This allows for the inclusion of Individual Subjects as factors in the model which adjusts for their individual differences. Briefly, the residuals produced by the GLMM are no longer differences from marginal means (group averages) but are taken from each subject's own personal average. Modeling the covariance matrix of residuals and adjusting for individual subjects can be done independently of one another or jointly. These models assume linearity and normality, which will be evaluated using Box-Cox and Shapiro-Wilk tests, respectively. Outliers and

influential cases will be screened for and removed. Violations of the assumptions will be remedied using transformations suggested by the Box-Cox test.

With the number of potential options for specifying a statistical model available, a best fitting model will be chosen based on the specifications that result in minimization of Akaike and Bayesian Information Criteria. These criteria allow for non-nested model comparisons. To simplify the discussion and interpretation of results for parameter estimates, the model that provided the best fit for the primary efficacy measures may be used uniformly for all results. It is anticipated that a number of different GLMMs will be evaluated to find the model that fits best, 1) a model including random intercepts, random slopes, and modeling the residual covariance structure; 2) a model including random intercepts and residual covariance structure; 3) a model including random intercepts; and lastly, 4) only modeling the covariance structure. The best fitting model will then be run including a Study Location random effect. If location is significant it will remain in the model to account for site differences, if it is not significant effect it will be removed for model parsimony.

Additional Analyses

In addition to the analyses for the primary outcome of gait speed (described above), an additional 2 x 2 x 5 GLMM will be performed using all trials and sessions, since 10MWT is collected for two trials, before and after the intervention, during each visit. This model will compare the change over time between groups across sessions. Adding the trial effect will allow us to test if there is within session learning, and may help establish the number of sessions that might be effective for participants in future studies.

Sequential moderated multiple regression analysis will be used to test if the effectiveness of the intervention is moderated by demographic (age, sex, race, etc.), biomechanical (initial walking speed, Cadence, Stride Length, Temporal Symmetry, and Spatial Symmetry), physiological (heart rate, blood pressure, respiration rate), and self-reported measures (QoL, and perceived disability). Both change in walking speed, GS_{Δ} , and percent change in walking speed, $GS_{\Delta per}$, will be used as outcomes. While this study is not powered for this, these results can help inform for whom this intervention is most effective and whom to target in future studies.

These regression models assume linearity, normality, homoscedasticity and no multicollinearity, these assumptions will be tested using Box-Cox, Shapiro-Wilk, Breusch-Pagan tests and examining the condition index and variance inflation factor, respectively. To eliminate ignorable collinearity caused by the inclusion of interaction terms, continuous variables will be centered before being entered into the models. Violations of the assumptions will be remedied using transformations suggested by the Box-Cox test.

13.2 Sample Size Justification

The study is powered for the primary outcomes, gait speed and percent change in Gait speed. Statistical power was set at 80% and the overall two-tailed alpha-level was set at .05. Approximately 78 participants will be prospectively enrolled at a minimum of three (3) sites with a target of 26 participants

per site. Allowing for 15% attrition and instrument failure, it is expected that 66 participants will complete the study, 33 in each group and 22 at each site. For the change in gait speed overtime between groups, this study is adequately powered (power = .80) to detect a moderately large to large effect ($d = .64$ to $.82$) for a plausible range of Intraclass correlation coefficients (ICCs), ($r = .05$ to $r = .20$), and conservative estimates of the correlation among repeated measures ($r = .4$ to $r = .6$) for $n = 66$ and $\alpha = .05$, see figure 4. For the percent change in gait speed, this study is adequately powered (power = .80) to detect a moderately large effect ($d = .62$ to $.67$) between groups for a plausible range of ICCs, ($r = .05$ to $r = .20$), for $n = 66$ and $\alpha = .05$, see figure 5. The ICCs here are an estimate of the percent of variation due to a site effect, without pilot data to garner these estimates a range of values were considered.

It has been shown that a good estimate of a potential standard deviation is the range/4.²³ In the absence of pilot data, further justification for this sample size is based on an article by by Flansbjer et al. in 2005. They found average gait speed of those with hemiparesis after stroke ranged from 0.4 to 1.4 and .4 to 1.5m/s in two different testing sessions, ranges of 1 and 1.1 respectively. This would give a standard deviation of gait speed of approximately .25, meaning this study could detect a difference in the change in gait speed between groups of .16 to .17 m/s (using d 's of .62 and .67) which are greater than the MCID of .15.

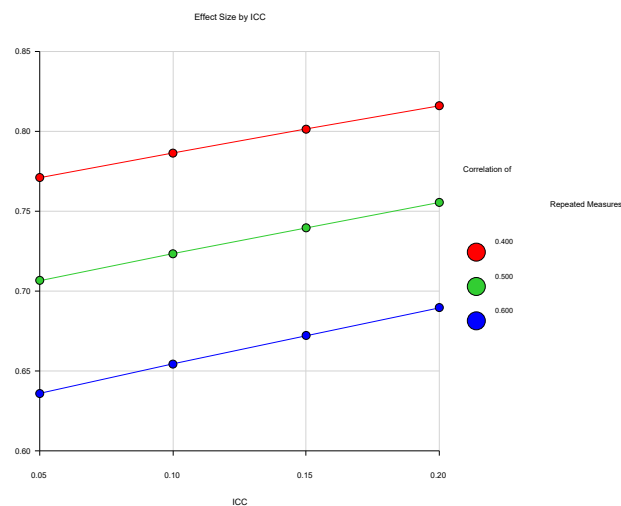


Figure 4. Effect Size (standardized difference in mean change over time) by ICC (variability due to site effects) and by Correlation Among Repeated Measures for Power = .8, $n = 66$, and $\alpha = .05$.

²³ Hozo, S. P., Djulbegovic, B., & Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC medical research methodology*, 5, 13. doi:10.1186/1471-2288-5-13

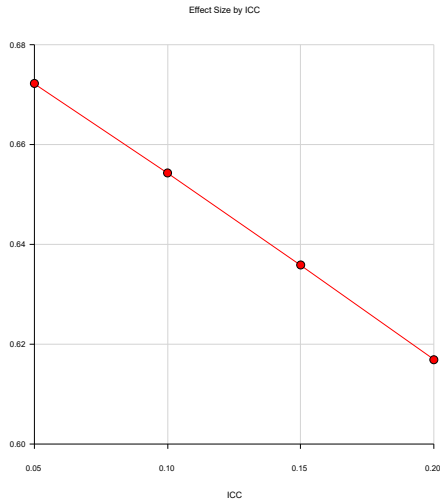


Figure 5. Effect Size (standardized difference in means) by ICC (variability due to site effects) for Power = .8, n=66, and alpha = .05.

Power calculations were performed for the secondary outcomes with a more conservative alpha (.01) to control for type-I error inflation from multiple hypothesis testing. For the chi-square and Mantel-Haenszel tests, this study is adequately powered (power = .80) with n = 66 and alpha = .01 to find a moderate effect (Cohen's $W = .4$) significant for $df = 1$. For the biomechanics and self-reported measures, a similar GLMM as for gait speed was used. This study is adequately powered (power = .80) to detect large effects ($d = .80$ to $d=1.00$) for a plausible range of Intraclass correlation coefficients (ICCs), ($r = .05$ to $r = .20$), and conservative estimates of the correlation among repeated measures ($r = .4$ to $r = .6$) for $n = 66$ and alpha = .05, see figure 6. For the correlation between biomechanical measures from the instrumented walkway and from the device, this study is adequately powered (power = .80), to detect correlations of .40 or larger, for $n = 66$, with alpha = .01.

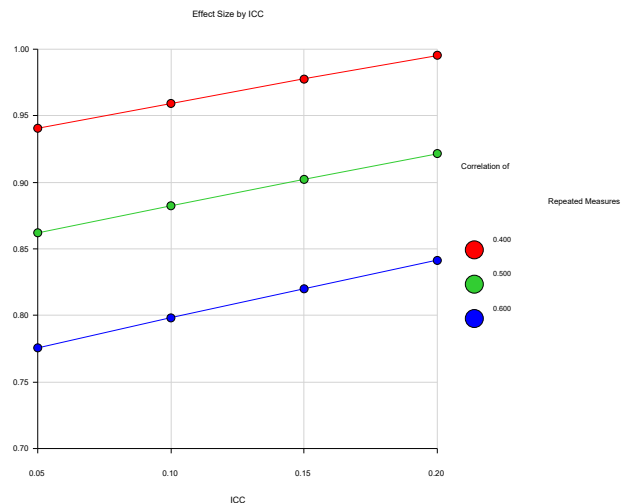


Figure 6. Effect Size (standardized difference in mean change over time) by ICC (variability due to site effects) and by Correlation Among Repeated Measures for Power = .8, n=66, and alpha = .01.

Subjects will continue to be enrolled until the targeted number of endpoints have been reached. When sufficient data has been collected to evaluate device performance, continued enrollment into the study will be assessed. The Sponsor retains the right to halt enrollment in the study when sufficient data has been collected to support the objectives of this study or it is determined that product performance is not likely to meet performance goals.

13.2.1 Statistical Considerations due to COVID-19

Due to the COVID-19 public health emergency, on March 17, 2020 study activities were put on hold due to mandates from the participating research institutions. The Sponsor engaged a consulting statistician to perform an unplanned, interim analysis. The interim analyses assessed the effectiveness of device with the data collected prior to the health emergency with the sole purpose of determining study feasibility if it were forced to end prior to reaching the initial sample size. In doing this, an estimate of the observed effect that was not available prior to the start of the study was made. Following the “Statistical Considerations for Clinical Trials During COVID-19,” posted by the FDA on June 2020, section B.3.b does indicate that interim analyses “could be potentially added to the original analysis plan for early stopping: (1) If a trial had no previous interim analyses, it may be possible to add an interim analysis plan.” It is recognized that the unplanned interim analysis might lead to a potential type-I error inflation. Following guidance of section B.6, a review discussion was initiated and the primary suggestion made by the FDA (adjusting alpha by half) will be complied with.

Considering the intended user population being at a far greater risk to complications from COVID-19^{24,25,26,27}, and when research activities for the study are able to resume at the participating institutions, the Sponsor intends to implement a newly planned interim analysis when a total of forty (40) participants are randomized into the study, which is approximately half of the anticipated enrollment. The interim analysis will follow the analysis plan as outlined in section 13.1; however, alpha will be set to 0.0125 for the primary outcomes. Due to the unplanned analysis, the original alpha of .05 was reduced by half. The remaining .025 to be spent across the rest of the trial. The newly planned interim and final analyses will use a conservative approach to the Pocock method. If a true Pocock alpha spending function were to be used with alpha = .025, the p-value for significance would be .0147. Using .0125 is being conservative with respect to type-I error inflation. If significance is found in the planned interim analysis that supports the objectives of this study, the Sponsor may use the results to support

²⁴ <https://publichealth.jmir.org/2020/2/e19462/#ref10>. Considerations for Postacute Rehabilitation for Survivors of COVID-19

²⁵ <http://europepmc.org/article/MED/32194034>. How Should the Rehabilitation Community Prepare for 2019-nCoV?

²⁶ <https://www.sciencedaily.com/releases/2020/05/200521124648.htm>. Stroke rates among COVID-19 patients are low, but cases are more severe

²⁷ https://www.nejm.org/doi/full/10.1056/NEJMc2009787?query=featured_home. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young

regulatory authorization to market the device. Additionally, the Sponsor intends to perform a poolability analysis to assess the comparability of patients enrolled before and after this trial modification. If those recruited after March 17, 2020 differ from those already collected, a pre vs. post COVID-19 variable will be included in the models to adjust for the difference.

All study staff involved in the conduct of the trial will remain blinded to results of the interim analysis to ensure the trial conduct will not be affected by the results.

14 INVESTIGATOR OBLIGATIONS

14.1 Guidelines for the Conduct of the Study

The Investigator is responsible for ensuring that the study is conducted in accordance with the clinical protocol and is in full compliance with FDA regulatory requirements; the basic principles outlined in 21 CFR Parts 11, 50, 54, 56 & 812, the ICH-Guidelines for Good Clinical Practice as published in the Federal Register on May 9, 1997 and the Declaration of Helsinki.

The Investigator is also responsible for protecting the rights, safety and welfare of Subjects under the Investigator's care.

14.2 Informed Consent

The Investigator or designee will inform the Subject of the nature, risks and purpose of the study. A written Informed Consent Form will be provided to each Subject describing this information. This form must be reviewed and approved by the Sponsor and the IRB before its use in the study. Each Subject must sign and date this form prior to their participation in the study.

A signed, original Consent Form for each Subject will be kept on file at the clinical site. A copy will also be given to the Subject signing the form.

14.3 Confidentiality

The Principal Investigator and designees, employees, and agents involved with this study will comply with relevant state and federal laws relating to the confidentiality, privacy and security of Subject's health information. They will only create, maintain, use or disclose any data that is generated by this study or other information disclosed to the Principal Investigator or their employees or agents during the course of the study to the Sponsor, IRB, FDA or other authorized recipients as appropriate for the execution, analysis, review and reporting of this study. Such information shall not be used for any other purposes and will remain confidential.

Study Subjects will be informed that all data collected for study purposes will be held in strict confidence and used for research purposes only. Records may be paper or electronic.

Paper Documents

Screening information (including NIH Stroke Scale), consent forms, HIPAA Authorizations and will be kept in paper format and stored in a locked file cabinet that only the study staff has access to. Study Subject files may also be scanned and stored on a secure, password-protected server authorized to store restricted data, with access provided only to the PI and key study staff.

De-Identified Study Subject ID Number

Data collected during this research will be labeled using a de-identified participant ID number.

Research Data

Data, including instrumented walkway data will be de-identified and stored on a secure, password-protected server. Data may be transferred as a local copy to password-protected study staff computers for processing or to prepare media material for publications, presentations or training purposes.

System Data

In addition to the data collected by the research equipment described above, the sensor platform will collect and store data related to the platform's performance on a secured cloud-based drive owned by MedRhythm's. Personally identifiable information will not be collected by the platform or stored by the company. Only the PI and a few designated study staff will have access to identifiable research data. The PI and all study staff will have access to all coded data housed on a password-protected secured network drive. No personally identifiable data will be shared with non-study personnel including students, professional colleagues, outside institutions or other study sponsors. No personally identifiable data will be used in scholarly presentations, in future research projects, product development and/or improvement, product registrations or in publications.

Privacy of participants will be protected by conducting all in-person interactions in a semi-private or private space within the rehabilitation laboratories. No personally identifiable information will be discussed in common areas.

Photos/Videos

Study Subjects will be asked to confirm their comfort with having photo/video taken during the testing (check off box in consent form). All video and photographic data that is taken will not contain any Study Subject names and will be stored on a password protected server with access limited to study staff.

Personal Health Information

Any personal health information in medical records obtained during the course of the study will be de-identified and labeled only with the Study Subject's alphanumeric study identifier. The HIPAA

Authorization for disclosure of protected health information will be kept with other participant information in a locked file cabinet accessible only to key study staff members.

14.4 Protocol Modification/Amendments

If preliminary or interim review indicates that modification should be made in the experimental design, study parameters, Subject selection, etc., these changes will be made after appropriate amendment(s) to this protocol with the mutual approval of the Sponsor and the Investigator. Any protocol change that may significantly affect the safety of study Subjects must also be submitted to the IRB for review and approval.

14.5 Recording & Monitoring of Study Data

System training, user names and passwords for accessing the internet-based EDC system will be provided to the study staff planning to input study data from source documentation into the electronic system. The data recorded on the CRFs must be derived from appropriate source documentation. Access to review and approve EDC forms will be provided to the Principal Investigator. The Investigator shall ensure that all data on the CRFs are complete, accurate and consistent with source documentation.

The MedRhythms' monitor (or designee) will review the CRFs for completeness and accuracy. Study data on the CRFs will be verified against information on original source documents in accordance with the monitoring plan. Source documentation may include, but is not limited to, clinical records, study-specific source documentation and may differ by site. The source documentation reviewed will be noted by the study monitor in each monitoring report. The monitor will also check the written Informed Consent Forms and all study specific logs for completeness, accuracy and plausibility.

14.6 Direct Access to Source Data & Study Documents

The Investigator and study center will permit trial-related monitoring, audits, IRB review and regulatory inspection by providing authorized personnel from the Sponsor, its representatives, the IRB, the FDA and other appropriate regulatory agency direct access to all trial-related data.

Direct access is the permission to examine, analyze, verify and reproduce any records, source documents or reports that are important to the evaluation of a clinical study. Any party with direct access should take reasonable precautions to maintain the confidentiality of the study Subjects and MedRhythms' proprietary information.

14.7 Remote Monitoring

Remote monitoring may be implemented at any time during the study at the discretion of the Sponsor. Remote monitoring involves verifying data elements submitted on CRFs against original source

documents and review of study administration logs, and must be conducted in accordance with the HIPAA Privacy Rule and site operating procedures. Note: only data submitted on CRFs is subject to remote monitoring.

The Investigator will facilitate remote access to original source documents and study logs using secure methods to transmit documents or providing copies of records that have been redacted or de-identified to protect personal health information. Facilitating access may also include locating physical records, providing secure electronic access to medical records systems, providing photocopied documentation, redacting paper records and /or uploading redacted source documents.

14.8 Record Retention

Data on the Case Report Forms, original Informed Consent Forms, original source documents, study records, and reports must be maintained by the Investigator for a period of five (5) years after the investigation is terminated or completed, or for a period of two (2) years after the records are no longer required for the purposes of supporting a pre-market approval application or a notice of completion of a product development protocol. MedRhythms should be notified in writing at least 30 days prior to the disposal or transfer to another location or party, of any study records related to this protocol.

APPENDIX A: INVESTIGATOR ACKNOWLEDGEMENT

Protocol Number: PS100

Version 5 Dated: 22 JUNE 2020

The following signature demonstrates approval of this protocol by MedRhythms, Inc.:

Brian Harris, CEO, MedRhythms

Name/Title

Signature/Date

INVESTIGATOR ACKNOWLEDGEMENT

I have read this protocol and agree that it contains all necessary details for me and my staff to conduct this study. I agree to personally conduct or supervise this study as outlined within the protocol. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments. I will provide all study personnel under my supervision, copies of the protocol and all relevant study information provided to me by MedRhythms, Inc. I will discuss this material with them to ensure that they are fully informed about the conduct of the trial.

I agree to ensure that the study will be conducted in accordance with the clinical protocol and in full compliance with FDA regulatory requirements outlined in 21 CFR Parts 11, 50, 54, 56 & 812, the International Conference on Harmonization (ICH) Topic E6: Guideline for Good Clinical Practice, and the Declaration of Helsinki. I agree to protect the rights, safety and welfare of Subjects under my care. I will ensure that the regulatory requirements for obtaining informed consent are met as required by 21 CFR Part 50. I agree to disclose to MedRhythms, Inc. accurate financial information as required by 21 CFR Part 54. I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

I agree to maintain adequate and accurate records in accordance with 21 CFR 812 Subparts E and G, and to make those records available for Sponsor monitoring, and general inspection in accordance with 21 CFR 812.145, as applicable. I agree to report to the Sponsor all adverse events that occur in the course of the investigation in accordance with 21 CFR 812.150(a)(1) as applicable.

Investigator Printed Name & Title: _____

Investigator Signature & Date: _____

Study Center Address: _____

Investigator Telephone Number: _____

Name(s) of Co/Sub-Investigators: _____