Promoting Recovery Optimization with WALKing Exercise After Stroke (PROWALKS)
NCT02835313
4/12/2023

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes
2. Original statistical analysis plan (excerpted from grant application, original IRB protocol, published study protocol), updates to statistical analysis plan (excerpted from final IRB protocol and from ClinicalTrials.gov registry)

Original approved IRB protocol 3/23/2016

HUMAN SUBJECTS PROTOCOL
University of Delaware

Protocol Title: Promoting Recovery Optimization with WALKing Exercise after Stroke (PROWALKS)

Principal Investigator
Name: Darcy Reisman, PT, PhD
Department/Center: Physical Therapy- STAR Campus
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Other Investigators:
Ryan Pohlig, PhD
David Edwards, PhD
Scott Kasner, MD (University of Pennsylvania)
Jonathan Raser-Schramm, MD, PhD (Christiana Care Health System)

Investigator Assurance:

By submitting this protocol, I acknowledge that this project will be conducted in strict accordance with the procedures described. I will not make any modifications to this protocol without prior approval by the IRB. Should any unanticipated problems involving risk to subjects occur during this project, including breaches of guaranteed confidentiality or departures from any procedures specified in approved study documents, I will report such events to the Chair, Institutional Review Board immediately.

1. **Is this project externally funded?** YES **X** NO

Grant revision is in review, with competitive score first cycle.

2. Research Site(s)

X University of Delaware

X Other (please list external study sites)
University of Pennsylvania
Christiana Care Health System

Is UD the study lead? **X** YES ☐ NO (If no, list the institution that is serving as the study lead)

3. **Project Staff**
Please list all personnel, including students, who will be working with human subjects on this protocol (insert additional rows as needed):

NAME	ROLE	HS TRAINING COMPLETE?
Darcy Reisman	PI	YES
Ryan Pohlig	Co-Investigator	YES
David Edwards	Co-Investigator	YES
Scott Kasner	Co-Investigator	YES
Jonathan Raser-Schramm	Co-Investigator	YES
Jennifer Marmon	Staff	YES
Kelly Danks	Research Physical Therapist	YES
Tamara Wright	Research Physical Therapist	YES

4. **Special Populations**
Does this project involve any of the following:

Research on Children? **NO**

Research with Prisoners? **NO**

If yes, complete the Prisoners in Research Form and upload to IRBNet as supporting documentation

Research with Pregnant Women? **NO**

Research with any other vulnerable population (e.g. cognitively impaired, economically disadvantaged, etc.)? please describe **NO**

5. **RESEARCH ABSTRACT** Please provide a brief description in LAY language (understandable to an 8th grade student) of the aims of this project.

The **overarching goal** of this research is to develop interventions that improve the overall health and quality of life of individuals post-stroke. As a group, stroke survivors are more physically inactive than even the most sedentary older adults. Lack of physical activity has serious consequences in persons with stroke, including an increased risk of recurrent stroke, developing other diseases and mortality. Current rehabilitation interventions do little to improve real-world walking activity after stroke, suggesting that simply improving walking capacity is not sufficient for improving daily physical activity after stroke. Rather, we hypothesize that the combination of a fast walking intervention that improves walking capacity, with a step activity monitoring program that facilitates translation of gains from the clinic to the "real-world", would generate greater improvements in real world walking activity than with either intervention alone. Data from our lab provides support for this hypothesis; however, it suggests that the greater efficacy of combining the 2 interventions depends on a participant's initial walking activity. Thus, *we do not expect that one intervention will be superior to the others for all participants*, but rather that the combined intervention will be superior for those with low levels of baseline walking activity, speed and endurance. The ***specific objective*** of this research is to test *whether and for whom* combining fast walking training with a step activity monitoring program (FAST+SAM) is superior in improving real-world walking activity compared to fast walking training alone (FAST) or a step activity monitoring and feedback program alone (SAM) in those with chronic stroke. Using a randomized controlled experimental design, 225 chronic (> 6 months) stroke survivors, will complete 12 weeks of fast walking training (FAST), a step activity

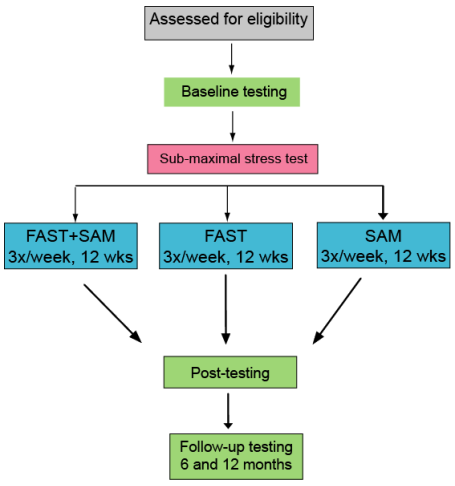
monitoring program (SAM) or a fast walking training + step activity monitoring program (FAST+SAM).The primary (steps per day), secondary (self-selected and fastest walking speed, walking endurance, oxygen consumption) and exploratory (vascular events, blood lipids, glucose, blood pressure) outcomes will be assessed by blinded evaluators prior to initiating treatment, after the last treatment and at a 6 and 12 month follow-up. Moderation of specific intervention outcomes by baseline characteristics will be evaluated to determine *for whom* the interventions are effective. Following completion of this study, we will not only understand the efficacy of the interventions and the individuals for which they are effective, we will have the necessary information to design a study investigating the secondary prevention benefits of improved physical activity post-stroke. This study is, therefore, an important step in the development of secondary prevention guidelines for persons with stroke.

6. **PROCEDURES**

258 adults with a past history of stroke will be recruited to participate in the study. The study will take place at 3 sites, the University of Delaware (UD), the University of Pennsylvania (UPenn) and Christiana Care Health System (CCHS). With a planned attrition rate of 13%, we anticipate 225 subjects will complete the study. Thus, approximately 86 subjects will be recruited at each of our 3 sites. See information regarding recruitment methods in #7 below. All testing and training (intervention) sessions will occur at UPenn and UD, while only training sessions will occur at CCHS with testing of CCHS subjects occurring at UD.

Regardless of recruitment method, during the initial phone call or email a member of the research team will describe the purpose and general procedures of the study. We will explain what to expect and the potential risks and benefits of participation. We will also inform the potential participant that joining the study is completely voluntary and that he/she is free to reconsider or stop participation at any time. If the potential participant expresses interest in agreeing to join, we will then proceed with a series of screening questions to determine if the person might be eligible (see Appendices).

Once potential eligibility for a participant is determined, medical approval for further screening and participation will be sought from the participant's physician, if it has not already been obtained (see IRBNet Protocol ID# 619037-1 in Appendices for details). Once medical approval is received the subject will be scheduled for the first evaluation session.



At the time of the first evaluation session, a member of the research team will first review the informed consent documents in detail with the potential participant. This will include a description of the study purpose and procedures, inclusion and exclusion criteria, the potential risks and benefits of participating, alternatives to participating, subjects' rights (such as withdrawal from the study, etc.) and compensation. The participant will be encouraged to ask questions and express concerns at any time during the consenting procedure or thereafter. If the participant agrees to be in the study, he/she will be asked to sign the informed consent document.

The figure illustrates the basic study design. Each evaluation session will last 2-3 hours and each training (intervention) session will last approximately 1 hour. There are a total of 8 evaluation sessions and 36 intervention sessions.

Testing Procedures

Baseline evaluation session. Subjects will undergo a brief battery of clinical assessments conducted by a trained member of the research team. Clinical assessments will include collection of medication and co-morbidity information, blood pressure, heart rate and body mass index, the 10 meter walk test, the 6 minute walk test, the Activities Specific Balance Confidence scale (ABC), the Patient Health Questionnaire nine-item depression scale (PHQ-9), and the Montreal Cognitive Assessment (MoCA) (see Appendices). In addition, subjects will be provided with a Fitbit activity monitor and instructed in its wear and use. Subjects will wear the monitor for 1 week. Following this baseline evaluation session and the 1 week step monitoring, the inclusion criteria of walking speed less than 1.0 m/s and steps/day less than 8000, can be evaluated and continued eligibility confirmed. If subjects do not meet these criteria after evaluation, they will be withdrawn from the study.

If any subject scores ≥5 on the PHQ-9, they will be informed of their score and advised to discuss this with their primary physician. In addition, for any participant endorsing suicidal ideation on one or more test items on PHQ-9, (1) we will notify the physician and (2) we will give the participant the telephone number for Crisis Intervention Services of Northern Delaware (302-577-2484 or 800-652-2929) which is staffed 24 hours/day, 7 days a week, to whom they can reach out if they feel desperate, hopeless and/or at risk for suicide. This is standard procedure for clients in the Physical Therapy Clinic.

Symptom limited graded exercise test. Prior to beginning the intervention, all subjects will undergo a symptom limited graded exercise test (GXT) on a motorized treadmill in the Nurse Managed Health Center (NMHC) under the supervision of a nurse practitioner and an exercise physiologist. During the GXT a12 lead electrocardiogram and breath by breath analysis of oxygen consumption with a metabolic cart will be recorded. The results of the test will be reviewed by a cardiologist for abnormal responses that would prevent the subject from safe participation.

Subjects will also have their blood drawn by a trained practitioner in the NHMC for measurement of blood lipids and glucose.

Post-intervention and follow-up evaluations. Post, 6 and 12 month evaluation sessions will be identical to the baseline evaluation including the graded exercise test for the purposes of measuring changes in oxygen consumption that may have occurred with the intervention and measurement of blood lipids and glucose.

In order to examine the potential secondary prevention benefits of the intervention, at the 6 and 12 month follow-up appointment subjects will be asked about major adverse cardiovascular and cerebrovascular events (MACCE)*;* specifically if they have had: recurrent stroke, myocardial infarction, unstable angina requiring hospitalization or peripheral artery event and the date of that event. This data will be confirmed for accuracy through contact with the subject's physician. Phone follow-up at 2 years will be completed for subjects enrolled in the first 2 years of the study to collect longer term follow-up data on these events. Information received from subjects will be confirmed by their physician (see Appendices). If subjects have any of these events during the course of the study, they will be withdrawn from all testing and training, except we will continue to track them for MACCE.

Intervention Procedures

Subjects will be randomly assigned to one of 3 groups: fast walking training (FAST), a step activity monitoring program (SAM) or a fast walking training + step activity monitoring program (FAST+SAM).

Walking training. All subjects in the FAST and FAST+SAM groups will complete walking training for 30 minutes, 3x/week for 12 weeks. These participants will complete a fast walking treadmill training program followed by approximately 10 minutes of over-ground walking activities. All treadmill walking will be completed while subjects wear an overhead chest-harness system for safety; no body weight support will be provided. Subjects will walk for 30 minutes with the goal of walking at the fast training speed, one at which Target Heart Rate (calculated using the Karvonen formula)[1] is achieved: (THR) = ((220-age) - Resting heart rate) x 80%)+ Resting heart rate[1]. The fast training speed interval is reduced if the subject requests to walk slower, the fast speed is no longer safe (e.g. increased toe scuffing or tripping), the subject reports a rate of perceived exertion of ≥17 on the 6-20 Borg Rate of Perceived Exertion Scale[2] and/if THR is exceeded. The treadmill speed is lowered to allow the heart rate to return to, ((220-age) – Resting heart rate) x 50-60%)+ Resting heart rate (Karvonen formula)[1], or to a rate of perceived exertion ≤13. If the HR is not steadily decreasing and the recovery criteria are not achieved within approximately 1 minute by walking slower, the treadmill is stopped and the subject takes a standing or seated rest break to achieve recovery. Once recovery is reached, the subject is transitioned to the fast training speed again.

Following treadmill walking, 10 minutes of over-ground walking activities are performed with the same THR and perceived exertion criteria as on the treadmill. Subjects are guarded and activities are progressed by a physical therapist. The purpose of this portion of the session is for the participant to practice walking activities experienced during everyday activities (e.g. turning, backward stepping, walking while carrying objects) to gain both skill and confidence with these routine walking activities that are important in real-world walking.

During training, the RPE[2] will be assessed every 2 minutes and heart rate will be continuously monitored. Blood pressure is tested prior to the initiation of any activity. It is also checked any time walking is stopped, including rest breaks, at the end of treadmill walking (prior to the start of over ground walking) and following over ground walking. For all sessions, the guidelines set forth by the American College of Sports Medicine for individuals in phase III or IV of cardiac rehabilitation will be followed[1]. Based on these guidelines, we have developed session termination criteria. A session will be terminated if any of the following occur:

- Drop in Systolic blood pressure of ≥ 10mmHg from baseline (resting for that day) despite increase in workload
- Hypertensive response with a systolic blood pressure >240 mmHg and diastolic blood pressure >110
- Presence of nervous system symptoms: ataxia, dizziness, or near syncope
- Any chest pain or angina symptoms
- Signs of poor perfusion cyanosis or pallor
- Excessive fatigue, excessive shortness of breath, leg cramps, claudication

If any of the above occurs, the subject's physician will be contacted and informed of the subject's response to the activity. Subjects can also terminate any session or training bout by stating their desire to stop.

Step activity monitoring program. Subjects in the SAM and FAST+SAM groups will participate in the step activity monitoring program and will be provided with a Fitbit. If the device is lost or damaged, it will be replaced to allow continued participation in the step activity monitoring program. Baseline step activity data for subjects in the FAST+SAM and SAM groups will be used to categorize and assign step activity goals. It is important to note that goals are set not based on an absolute number for all subjects, but rather individually, based on their own baseline walking. Goals are advanced based on subject achievement of previous goals. For subjects in the FAST+SAM group, step activity data is reviewed at each treadmill training session and used to determine and promote goal achievement. Subjects in the SAM group will visit the clinic 3x/week for this review. Step activity data in the interim days between sessions will reviewed and used to assist subjects in understanding how much walking activity they performed during certain daily activities, like walking to the mailbox or walking laps around their home, and how that added to their total steps per day. Subjects are also advised of how their steps per day related to goal achievement; a discussion of individualized ideas to increase activity and of any barriers and how to overcome those barriers occurred. These discussions have been shown to be critical for the success of a step activity monitoring program. Subjects in the FAST group will be instructed not to begin the use of a step monitor during the study.

7. STUDY POPULATION AND RECRUITMENT

Recruitment and Enrollment Procedures:

Subjects will be recruited from a variety of sources. For recruitment at the University of Delaware we will utilize the University of Delaware Stroke Studies Registry, a database of stroke survivors who are interested in participating in research. The use and maintenance of the Registry is described in detail in IRBNet Protocol ID# 619037-1, entitled "Shared Pre-enrollment Process for Stroke Research Team Studies", PI Reisman, Co-PI Morton (see Appendices). People are recruited and phone-screened through this protocol. Additionally, medical clearance from the acting physician is also obtained through this protocol. Individuals from the registry who appear likely to meet eligibility requirements will be contacted by telephone. See details of registry protocol procedures in attached Appendices. In addition, other persons with stroke will be recruited via local physical therapy practices, physicians' offices and support groups. Other recruiting could occur through the PI(s) public speaking engagements or by word of mouth from visitors to the lab or past participants in stroke studies.

Describe what exclusionary criteria, if any will be applied.

The specific subject inclusion and exclusion criteria are:
Inclusion Criteria: 1) Age 21-85, 2) Chronic stroke (>6 months post stroke), 3) Able to walk at self-selected speed without assistance from another person (assistive devices are allowed), 4) Self-selected walking speed <1.0 m/s, 5) Average steps/day <8,000, 6) Resting heart rate between 40-100 beats per minute, 5) Resting blood pressure between 90/60 to 170/90. **Exclusion Criteria:** 1) Evidence of cerebellar stroke, 2) Other potentially disabling neurologic conditions in addition to stroke, 3) Lower limb Botulinum toxin injection <4 months earlier, 4) Current participation in physical therapy, 5) Inability to walk outside the home prior to the stroke, 5) Coronary artery bypass graft, stent placement or myocardial infarction within past 3 months, 6) Musculoskeletal pain that limits activity, 7) Inability to communicate with investigators, 8) score >1 on question 1b and >0 on question 1c on the NIH Stroke Scale.

The inclusion and exclusion criteria are discussed at the initial screening and again on the first testing day when the informed consent document is reviewed. Determining whether all criteria on the Inclusion and Exclusion Criteria Checklist (see Appendices) are met is based on a

combination of subjects' individual responses and information from other documentation. Two inclusion criteria (walking speed <1.0 m/s and steps per day <8,000) cannot be evaluated until the baseline evaluation is completed. Therefore, subjects will be withdrawn from the study if these criteria are not met following this evaluation.

Describe what (if any) conditions will result in PI termination of subject participation.

Participation in the study is voluntary. Any subject may withdraw from the study at any time without any negative consequences. In addition, the PI may terminate a subject's participation if the subject is viewed by the PI to be placing him/herself at risk. This is not expected, but could potentially occur. Similarly, the subject may be withdrawn from the study based on abnormal results identified on the symptom-limited graded exercise test.

8. **RISKS AND BENEFITS**

List all potential physical, psychological, social, financial or legal risks to subjects (risks listed here should be included on the consent form).

Participation in any physical activity or exercise has risk. These risks include but are not limited to, pain, fainting, dizziness, fatigue, nausea, shortness of breath, chest pain or angina, myocardial infarction, swelling, bruising, muscle/bone/joint soreness, joint damage, bone fracture, ligament/tendon/connective tissue damage, hospitalization, and death.

Psychological risks include possible discomfort, frustration, and/or anxiety related to difficulty with the physical testing or completion of questionnaires.

Graded exercise testing carries a low risk of myocardial infarction/cardiac arrest (1/2500; ACC/AHA) and patients will be made aware of this risk prior to testing. However, graded exercise testing is a standard procedure for diagnostic purposes, evaluation of functional capacity, and the effectiveness of both exercise and pharmacological interventions.

The risks of taking blood include pain and/or bruising where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

In your opinion, are risks listed above minimal* or more than minimal? If more than minimal, please justify why risks are reasonable in relation to anticipated direct or future benefits.

The risks of the study are not more than minimal.

What steps will be taken to minimize risks?

During treadmill walking subjects are allowed rest breaks whenever requested or deemed appropriate by the experimenter. Because participants who have sustained a stroke may be at increased cardiovascular risk, when a potential post-stroke participant contacts the team, they will be asked to provide consent to allow the investigators to contact the referring or primary physician to obtain medical clearance for participation. Potential participants will only be brought to the laboratory for testing once this clearance has been obtained. Prior to the initiation of training, all subjects will undergo a 12 lead symptom limited graded exercise test reviewed by a cardiologist. All subjects will wear a heart rate monitor during testing and training. During all treadmill walking, subjects will wear a harness connected to an overhead support. During walking training, the Borg Scale of perceived exertion (RPE) [1] will be measured every 2 minutes and heart rate will be continuously monitored. For all training sessions, the guidelines

set forth by the American College of Sports Medicine (ACSM) for individuals in phase III or IV of cardiac rehabilitation will be followed. Based on these guidelines, a session will be terminated if any of the following conditions occur:

- Drop in Systolic blood pressure of ≥ 10mmHg from baseline (resting for that day) despite increase in workload
- Hypertensive response with a systolic blood pressure >240 mmHg and diastolic blood pressure >110
- Presence of nervous system symptoms: ataxia, dizziness, or near syncope
- Any chest pain or angina symptoms
- Signs of poor perfusion cyanosis or pallor
- Excessive fatigue, excessive shortness of breath, leg cramps, claudication

If any of the above occurs, the subject's physician will be contacted and informed of the subject's response to the activity. Subjects can also terminate any session or training bout by stating their desire to stop.

Any incidents involving injury to study subjects will be presented to the Data and Safety Monitoring Board and the IRB immediately. Please see information related to the Data and Safety Monitoring Board below.

Describe any potential direct benefits to participants.
The direct benefit to the subjects participating in training could be substantial. Previous research has shown that 12 weeks of treadmill training can lead to improvements in walking speed and activity. So regardless of the effects of our specific intervention, subjects are likely to obtain some benefit of participation. This will be explained to all subjects. The methods of study will provide sensitive, objective measures of walking function and activity, which would be useful in monitoring progress, or the lack of it, across time and therapy. This will be explained to all subjects.

Describe any potential future benefits to this class of participants, others, or society.

The potential benefits of this study are that we may understand mechanisms and interventions to improve physical activity in chronic stroke survivors. The knowledge gained will provide an understanding of the optimal characteristics of rehabilitation interventions to promote functional walking recovery post stroke. Because of the potential for these results to lead to development of new approaches to rehabilitation interventions for stroke survivors that could significantly impact secondary prevention of future stroke and other conditions, the potential benefits far outweigh the minimal risks.

If there is a Data Monitoring Committee (DMC) in place for this project, please describe when and how often it meets.
There is a Data and Safety Monitoring Board (DSMB) for this study. Please see the description of the example DSMB Charter in the Appendices.

9. **COMPENSATION**

Will participants be compensated for participation? Yes.

If so, please include details.

Subjects will be paid $100.00 for participation, $25.00 after each of the evaluation time points is completed.

Participants are responsible for transportation to the study site for each visit. In some situations, if a participant cannot arrange transportation alone, transportation will be arranged for them.

10. **DATA**
Will subjects be anonymous to the researcher?

Subjects will not be anonymous to the researchers. As part of the consent process and verification of eligibility, subjects must provide their name, date of birth and other identifying information to members of the research team. However, identities will be kept confidential to the extent possible (see Confidentiality section below). De-identified data may be presented in abstract, poster, presentation, or published manuscript format.

If subjects are identifiable, will their identities be kept confidential? (If yes, please specify how)

Subject identities will be kept confidential by assigning each subject a number.

How will data be stored and kept secure (specify data storage plans for both paper and electronic files. For guidance see http://www.udel.edu/research/preparing/datastorage.html)

All data sheets will be stored in the subject's folder in a locked file cabinet. Encrypted electronic data will be stored in a database on a password protected UD managed server. Identifiable data will be shared between sites through this database. Paper copies of consent forms for each site will be stored on-site. Electronic copies of consents will be encrypted and placed on a UD managed password protected server.

How long will data be stored?

All de-identified data will be stored indefinitely and may be used in future research studies.

Will data be destroyed? **X** YES ☐ NO (if yes, please specify how the data will be destroyed)
Data with identifying information will be saved until the project is complete or the data are published, whichever comes first and then the identifiable data will be destroyed. This will involve all electronic data being wiped from hard-drives and servers and all paper data being shredded. Raw de-identified data will be stored indefinitely and may be used in future related studies.

Will the data be shared with anyone outside of the research team? **X** YES NO

These data will be used by the current investigative team, and then, in compliance with NIH policy, shared with others through the NICHD DASH repository so that additional analyses can be performed. Once the primary hypotheses of the current proposal are tested, all data will be

cleaned, de-identified, and be deposited in the DASH repository. To ensure that the identities of research subjects cannot be readily ascertained with the data, NICHD DASH will store only data that are without identifiers and coded. According to NICHS DASH requirements, before submitting the data to NICHD DASH, investigators must:

a. Strip the data of individually identifying information according to:
    - the standards set forth in the HHS Regulations for the Protection of Human Subjects and related guidance (which covers individually identifiable private information), and
    - the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (which covers protected health information); and
b. Assign to the de-identified data random, unique codes.

How will data be analyzed and reported?

Appropriate statistical analysis of the primary (General Linear Mixed Modeling) and exploratory (Cox Proportional Hazards Model and a Generalized Estimating Equation) outcomes will be completed under the direction of the biostatistician on the project. The results will be reported to professionals interested in research via journals and presentations.

11. **CONFIDENTIALITY**
Will participants be audiotaped, photographed or videotaped during this study?

Individual subjects may be approached and asked to be photographed or videotaped for recruitment, educational or research purposes. A photo release form will be signed by participants prior to any photographs or videotape taken. Subjects will be told that this is an optional activity and not a requirement of participation. Photographs or video will have the face covered.

How will subject identity be protected?

All participants' identifying information will be stored in a locked file cabinet (paper forms) or on password-protected computers or servers (electronic forms) and will be utilized only by investigators on the protocol who have a specific need for the identifying information. All data collection sheets and all data will be de-identified and, instead, coded using a numerical system, the key to which will be maintained on a password-protected computer. These de-identified data and data collection sheets will also be stored in a locked file cabinet (paper forms) or on password-protected computers or servers (electronic forms) that are kept separate from the identifying information.

Is there a Certificate of Confidentiality in place for this project? (If so, please provide a copy).

There is no Certificate of Confidentiality in place for this project.

12. **CONFLICT OF INTEREST**
(For information on disclosure reporting see: http://www.udel.edu/research/preparing/conflict.html)

Do you have a current conflict of interest disclosure form on file through UD Web forms? Yes
Does this project involve a potential conflict of interest*? NO

* As defined in the University of Delaware's Policies and Procedures ,a potential conflict of interest (COI) occurs

when there is a divergence between an individual's private interests and his or her professional obligations, such that an independent observer might reasonably question whether the individual's professional judgment, commitment, actions, or decisions could be influenced by considerations of personal gain, financial or otherwise.

If yes, please describe the nature of the interest:

13. **CONSENT and ASSENT**

___X_ Consent forms will be used and are attached for review (see Consent Template under Forms and Templates in IRBNet)

____ Additionally, child assent forms will be used and are attached.

____ Waiver of Documentation of Consent (attach a consent script/information sheet with the signature block removed).

____ Waiver of Consent (Justify request for waiver)

14. **Other IRB Approval**
Has this protocol been submitted to any other IRBs? Not yet, but it will be submitted to the University of Pennsylvania and Christiana Care Health System IRBs.

15. **Supporting Documentation**
Please list all additional documents uploaded to IRBNet in support of this application.

Appendices which include IRBNet Protocol ID# 619037-1, entitled “Shared Pre-enrollment Process for Stroke Research Team Studies”, that is referenced in this protocol, along with copies of specific clinical tests, screening questions and the inclusion/exclusion checklist for this protocol.

A separate Appendix is attached with the example DSMB charter.

REFERENCES

1. 7th ed. Philadelphia: Lippincott, Williams and Wilkines; 2006. American College Of Sports Medicine (ACSM) – Guidelines for exercise testing and prescription.
2. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2(2):92-8.

Final approved IRB protocol
3/13/2023

HUMAN SUBJECTS PROTOCOL
University of Delaware

Protocol Title: Promoting Recovery Optimization with WALKing Exercise after Stroke (PROWALKS)

Principal Investigator
Name: Darcy Reisman, PT, PhD
Department/Center: Physical Therapy- STAR Campus
Contact Phone Number: 302-831-0508
Email Address: dreisman@udel.edu

Other Investigators:
Ryan Pohlig, PhD
David Edwards, PhD

Investigator Assurance:

By submitting this protocol, I acknowledge that this project will be conducted in strict accordance with the procedures described. I will not make any modifications to this protocol without prior approval by the IRB. Should any unanticipated problems involving risk to subjects occur during this project, including breaches of guaranteed confidentiality or departures from any procedures specified in approved study documents, I will report such events to the Chair, Institutional Review Board immediately.

1. **Is this project externally funded? X**YES NO
   PHYT322245

2. Research Site(s)

X University of Delaware

X Other (please list external study sites)
Christiana Care Health System
Indiana University

Is UD the study lead? **X** YES ☐ NO (If no, list the institution that is serving as the study lead)

3. **Project Staff**
Please list all personnel, including students, who will be working with human subjects on this protocol (insert additional rows as needed):

NAME	ROLE	HS TRAINING COMPLETE?
Darcy Reisman	PI	YES
Ryan Pohlig	Co-Investigator	YES
David Edwards	Co-Investigator	YES
Jennifer Marmon	Staff	YES
Alicia Adkins	Staff	YES
Tamara Wright	Research Physical Therapist	YES
Henry Wright	Research Physical Therapist	Yes
Martha Callahan	Staff	YES
Jane Diehl	Staff	YES
Elizabeth Thompson	Research Scientist	Yes
Kiersten McCartney	Student Researcher	YES
Kenna Gilley	Staff	Yes

4. **Special Populations**
Does this project involve any of the following:

Research on Children? **NO**

Research with Prisoners? **NO**

If yes, complete the Prisoners in Research Form and upload to IRBNet as supporting documentation

Research with Pregnant Women? **NO**

Research with any other vulnerable population (e.g. cognitively impaired, economically disadvantaged, etc.)? please describe **NO**

5. **RESEARCH ABSTRACT** Please provide a brief description in LAY language (understandable to an 8th grade student) of the aims of this project.

The **overarching goal** of this research is to develop interventions that improve the overall health and quality of life of individuals post-stroke. As a group, stroke survivors are more physically inactive than even the most sedentary older adults. Lack of physical activity has serious consequences in persons with stroke, including an increased risk of recurrent stroke, developing other diseases and mortality. Current rehabilitation interventions do little to improve real-world walking activity after stroke, suggesting that simply improving walking capacity is not sufficient for improving daily physical activity after stroke. Rather, we hypothesize that the combination of a fast walking intervention that improves walking capacity, with a step activity monitoring program that facilitates translation of gains from the clinic to the "real-world", would generate greater improvements in real world walking activity than with either intervention alone. Data from our lab provides support for this hypothesis; however, it suggests that the greater efficacy of combining the 2 interventions depends on a participant's initial walking activity. Thus, *we do not expect that one intervention will be superior to the others for all participants*, but rather that the combined intervention will be superior for those with low levels of baseline walking activity, speed and endurance. The ***specific objective*** of this research is to test *whether and for whom* combining fast walking training with a step activity monitoring program

(FAST+SAM) is superior in improving real-world walking activity compared to fast walking training alone (FAST) or a step activity monitoring and feedback program alone (SAM) in those with chronic stroke. Using a randomized controlled experimental design, 225 chronic (> 6 months) stroke survivors, will complete approximately 12 weeks (goal of 36 sessions) of fast walking training (FAST), a step activity monitoring program (SAM) or a fast walking training + step activity monitoring program (FAST+SAM).The primary (steps per day), secondary (self-selected and fastest walking speed, walking endurance, oxygen consumption) and exploratory (vascular events, blood lipids, glucose, blood pressure) outcomes will be assessed by blinded evaluators prior to initiating treatment, after the last treatment and at a 6 and 12 month follow-up. Moderation of specific intervention outcomes by baseline characteristics will be evaluated to determine *for whom* the interventions are effective. Following completion of this study, we will not only understand the efficacy of the interventions and the individuals for which they are effective, we will have the necessary information to design a study investigating the secondary prevention benefits of improved physical activity post-stroke. This study is, therefore, an important step in the development of secondary prevention guidelines for persons with stroke.

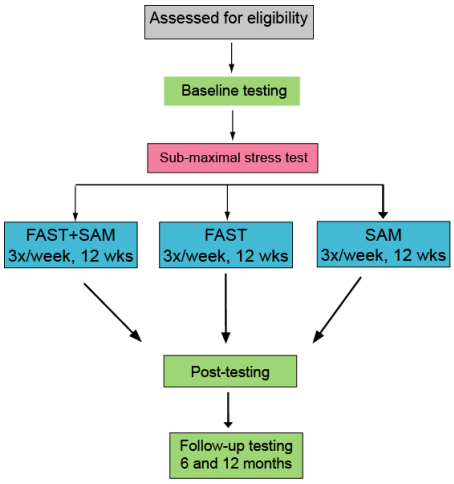
6. **PROCEDURES**

750 adults with a past history of stroke will be recruited to participate in the study. The study will take place at 4 sites, the University of Delaware (UD), the University of Pennsylvania (UPenn), Christiana Care Health System (CCHS) and Indiana University (IU). We anticipate 225 subjects will complete the study. The number recruited at each study site will be flexible as recruitment varies across sites. Subject numbers are monitored on an ongoing basis through the REDCap database. See information regarding recruitment methods in #7 below. All testing and training (intervention) sessions will occur at IU, UPenn and UD, while only training sessions will occur at CCHS with testing of CCHS subjects occurring at UD. Data collection sessions at the University of Pennsylvania were ended as of July 2020, but analysis of data collected at that site will continue through the end of the project.

We may recruit participants from the University of Delaware Stroke Research Registry (IRB# 1642798). Please see attached Study Approval Letter. Participants recruited through other means will be offered the opportunity to enroll in the Stroke Research Registry when they consent to this study. Lab members will be instructed to emphasize that enrolling in the Registry is completely voluntary and the participant's choice to enroll or not has no effect on their participation in this study or any other studies conducted at the University of Delaware.

Regardless of recruitment method, during the initial phone call or email a member of the research team will describe the purpose and general procedures of the study. We will explain what to expect and the potential risks and benefits of participation. We will also inform the potential participant that joining the study is completely voluntary and that he/she is free to reconsider or stop participation at any time. If the potential participant expresses interest in agreeing to join, we will then proceed with a series of screening questions to determine if the person might be eligible (see Appendices). For subjects that do not appear to be eligible, screening forms will be destroyed. No additional documentation (e.g.- consent forms, HIPPA forms) will be handled by UD in regards to UPenn or IU subjects.

Once potential eligibility for a participant is determined, subjects will be scheduled for PRE Clinical Baseline Testing. During the PRE Clinical Baseline Testing, subjects will fill out the PROWALKS Consent form, the Stroke Registry Consent form and the PROWALKS Medical Clearance formThe medical clearance must be completed prior to participating in the submaximal stress test. Medical clearance can be given verbally to a Stroke Team member following discussion with the provider. The medical clearance form will be noted to indicate the information that was provided verbally, along with the date of the receipt of that information, the provider's name, and the signature of the person obtaining the information. If we become aware of a new medical issue with a participant that would likely impact their participation in future studies we will relay this information for inclusion in the Stroke Research Registry (IRBNet Protocol ID# 1642798, Stroke Research Registry) so that other investigators potentially interested in recruiting this person into a different study are aware.



At the time of the first evaluation session, a member of the research team will first review the informed consent documents in detail with the potential participant. This will include a description of the study purpose and procedures, inclusion and exclusion criteria, the potential risks and benefits of participating, alternatives to participating, subjects' rights (such as withdrawal from the study, etc.) and compensation. The participant will be encouraged to ask questions and express concerns at any time during the consenting procedure or thereafter. If the participant agrees to be in the study, he/she will be asked to sign the informed consent document.

The figure illustrates the basic study design. Each evaluation session will last 1-3 hours and each training (intervention) session will last approximately 1 hour. There are a total of 8-12 evaluation sessions and 36 intervention sessions.

Testing Procedures

Baseline evaluation session. Subjects will undergo a brief battery of clinical assessments conducted by a trained member of the research team. Clinical assessments will include collection of medication and co-morbidity information, blood pressure, heart rate and body mass index, the 10 meter walk test, the 6 minute walk test, the Activities Specific Balance Confidence scale (ABC), the Patient Health Questionnaire nine-item depression scale (PHQ-9), and the Montreal Cognitive Assessment (MoCA) (see Appendices). In addition, subjects will be provided with a Stepwatch Activity Monitor and/or Fitbit activity monitor and instructed in its wear and use. Subjects will wear the monitor for 1 week. Following this baseline evaluation session and the 1 week step monitoring, the inclusion criteria of walking speed between 0.3 and 1.0 m/s and steps/day less than 8000, can be evaluated and continued eligibility confirmed. If subjects do not meet these criteria after evaluation, they will be withdrawn from the study.

If any subject scores ≥5 on the PHQ-9, they will be informed of their score and advised to discuss this with their primary physician. In addition, for any participant endorsing suicidal ideation on one or more test items on PHQ-9, (1) we will notify the physician and (2) we will give the participant the telephone number for Crisis Intervention Services of Northern Delaware (302-577-2484 or 800-652-2929) which is staffed 24 hours/day, 7 days a week, to whom they can reach out if they feel desperate, hopeless and/or at risk for suicide. This is standard procedure for clients in the Physical Therapy Clinic.

Symptom limited graded exercise test. Prior to beginning the intervention, all subjects will undergo a symptom limited graded exercise test (GXT) on a motorized treadmill in the Nurse Managed Health Center (NMHC) under the supervision of a nurse practitioner and an exercise physiologist. During the GXT a12 lead electrocardiogram and breath by breath analysis of oxygen consumption with a metabolic cart will be recorded. The results of the test will be reviewed by a cardiologist for abnormal responses that would prevent the subject from safe participation.

Subjects will have up to 5 ml of blood drawn by a trained practitioner in the NHMC for measurement of blood lipids and glucose at each of the testing time points (baseline, post-intervention and 6 and 12 month follow-up evaluation sessions).

Post-intervention and follow-up evaluations. Post, 6 and 12 month evaluation sessions will be identical to the baseline evaluation including the graded exercise test for the purposes of measuring changes in oxygen consumption that may have occurred with the intervention and measurement of blood lipids and glucose.

In order to examine the potential secondary prevention benefits of the intervention, at the 6 and 12 month follow-up appointment subjects will be asked about major adverse cardiovascular and cerebrovascular events (MACCE)*;* specifically if they have had: recurrent stroke, myocardial infarction, unstable angina requiring hospitalization or peripheral artery event and the date of that event. This data will be confirmed for accuracy through contact with the subject's physician. Phone follow-up at 2 years will be completed for subjects enrolled in the first 2 years of the study to collect longer term follow-up data on these events. Information received from subjects will be confirmed by their physician (see Appendices). If subjects have any of these events during the course of the study, they will be withdrawn from all testing and training, except we will continue to track them for MACCE.

Decisions will be made regarding withdrawing subjects at 6 and 12 months by gathering medical record information as needed for subjects who report changes in their health history. Self-reported and non-physical measures may still be collected at 6 and 12 month time points even if they are not able to perform physical testing.

In addition to the 6 and 12 month follow-up, subjects will be contacted by the Stroke Studies Coordinator at UD at 4.5, and 9 months post baseline testing to check in as a means to improve subject retention. Subjects will be told that we are calling to check in. We will ask them if anything has changed since their last visit/phone call, including address, contact information, physician. Any changes in this information will be updated in the database.

Intervention Procedures

Subjects will be randomly assigned to one of 3 groups: fast walking training (FAST), a step activity monitoring program (SAM) or a fast walking training + step activity monitoring program (FAST+SAM).

Walking training. All subjects in the FAST and FAST+SAM groups will complete walking training for 30 minutes, with a goal of 3x/week for 12 weeks. These participants will complete a fast walking treadmill training program followed by approximately 10 minutes of over-ground walking activities. All treadmill walking will be completed while subjects wear an overhead chest-harness system for safety; no body weight support will be provided. Subjects will walk for 30 minutes with the goal of walking at the fast training speed, one at which Target Heart Rate (calculated using the Karvonen formula)[1] is achieved: (THR) = ((max HR found on GXT) - Resting heart

rate) x 80%)+ Resting heart rate[1]. The fast training speed interval is reduced if the subject requests to walk slower, the fast speed is no longer safe (e.g. increased toe scuffing or tripping), the subject reports a rate of perceived exertion of ≥17 on the 6-20 Borg Rate of Perceived Exertion Scale[2] and/if THR is exceeded. The treadmill speed is lowered to allow the heart rate to return to, ((max HR found on GXT) – Resting heart rate) x 50-60%)+ Resting heart rate (Karvonen formula)[1], or to a rate of perceived exertion ≤13. If the HR is not steadily decreasing and the recovery criteria are not achieved within approximately 1 minute by walking slower, the treadmill is stopped and the subject takes a standing or seated rest break to achieve recovery. Once recovery is reached, the subject is transitioned to the fast training speed again.

Following treadmill walking, 10 minutes of over-ground walking activities are performed with the same THR and perceived exertion criteria as on the treadmill. Subjects are guarded and activities are progressed by a physical therapist. The purpose of this portion of the session is for the participant to practice walking activities experienced during everyday activities (e.g. turning, backward stepping, walking while carrying objects) to gain both skill and confidence with these routine walking activities that are important in real-world walking.

During training, the RPE[2] will be assessed every 2 minutes and heart rate will be continuously monitored. Blood pressure is tested prior to the initiation of any activity. It is also checked at the Research PT's discretion any time walking is stopped, including rest breaks, at the end of treadmill walking (prior to the start of over ground walking) and following over ground walking. For all sessions, the guidelines set forth by the American College of Sports Medicine for individuals in phase III or IV of cardiac rehabilitation will be followed[1]. Based on these guidelines, we have developed session termination criteria. A session will be terminated if any of the following occur:

- Drop in Systolic blood pressure of ≥ 10mmHg from baseline (resting for that day) despite increase in workload
- Hypertensive response with a systolic blood pressure >240 mmHg and diastolic blood pressure >110
- Presence of nervous system symptoms: ataxia, dizziness, or near syncope
- Any chest pain or angina symptoms
- Signs of poor perfusion cyanosis or pallor
- Excessive fatigue, excessive shortness of breath, leg cramps, claudication

If any of the above occurs, the subject's physician will be contacted and informed of the subject's response to the activity. Subjects can also terminate any session or training bout by stating their desire to stop.

Step activity monitoring program. Subjects in the SAM and FAST+SAM groups will participate in the step activity monitoring program and will be provided with a Stepwatch Activity Monitor and/or Fitbit. If the device is lost or damaged, it will be replaced to allow continued participation in the step activity monitoring program. Baseline step activity data for subjects in the FAST+SAM and SAM groups will be used to categorize and assign step activity goals. It is important to note that goals are set not based on an absolute number for all subjects, but rather individually, based on their own baseline walking. Goals are advanced based on subject achievement of previous goals. For subjects in the FAST+SAM group, step activity data is reviewed at each treadmill training session and used to determine and promote goal achievement. Subjects in the SAM group will visit the clinic 3x/week for this review. Step activity data in the interim days between sessions will reviewed and used to assist subjects in

understanding how much walking activity they performed during certain daily activities, like walking to the mailbox or walking laps around their home, and how that added to their total steps per day. Subjects are also advised of how their steps per day related to goal achievement; a discussion of individualized ideas to increase activity and of any barriers and how to overcome those barriers. These discussions have been shown to be critical for the success of a step activity monitoring program.
Subjects in the FAST group will be instructed not to begin the use of a step monitor during the study.

7. **STUDY POPULATION AND RECRUITMENT**

Recruitment and Enrollment Procedures:

Subjects will be recruited from a variety of sources. For recruitment at the University of Delaware we will utilize the University of Delaware Stroke Studies Registry, a database of stroke survivors who are interested in participating in research. The use and maintenance of the Registry is described in detail in IRBNet Protocol ID# 619037-1, entitled “Shared Pre-enrollment Process for Stroke Research Team Studies”, PI Reisman, Co-PI Morton (see Appendices). People are recruited and phone-screened through this protocol. Additionally, medical opinion of fitness to participate in research form is obtained from the acting physician through this protocol. Individuals from the registry who appear likely to meet eligibility requirements will be contacted by telephone. See details of registry protocol procedures in attached Appendices. In addition, other persons with stroke will be recruited via local physical therapy practices, physicians’ offices and support groups. Other recruiting could occur through the PI(s) public speaking engagements or by word of mouth from visitors to the lab or past participants in stroke studies.

Recruitment will also take place through the Christiana Care Portal and Focus. The portal is the internal Christiana Care Home Page with internal breaking news and announcements of interest across the organization. All CCHS employees would see this. The FOCUS, is a biweekly publication distributed to CCHS employees, volunteers, and retirees of Christiana Care Health System. Recruitment will also include contact of CCHS patients who have been admitted in the CCHS system with a diagnosis of stroke (See Appendix I for CCHS documentation that allows for contact of patients for research).

If the potential participant is found to be interested and potentially eligible, we will schedule an appointment for the laboratory testing. In addition, the participant’s primary care physician will be contacted to obtain the Medical opinion of fitness to participate in research form for full participation in the study if it has not already been obtained (see IRBNet Protocol ID# 619037-1 in Appendices for details). This form is reviewed upon receipt. If it is noted that the medical provider does not check off either "Any serious cardiovascular or cardiopulmonary condition preventing participation" or "Any serious musculoskeletal or other medical condition preventing participation" on the Medical opinion of fitness to participate in research form, the potential participant will be scheduled for participation in the study. If the medical provider does check off either "Any serious cardiovascular or cardiopulmonary condition preventing participation" or "Any serious musculoskeletal or other medical condition preventing participation" on the form, a member of the research team will contact the medical provider to get more information on the specific medical condition, if it is not provided on the form. If appropriate, the investigator will provide specific information regarding the study protocol to the medical provider. If, after this conversation, the medical provider no longer feels there are any serious conditions preventing participation, this will be indicated on the form and the potential participant will be scheduled for the study.

Medical records may also be obtained for CCHS and UD subjects via the DHIN (Delaware Health Information Network) if subjects agree to this when signing the HIPAA form. These records for PROWALKS subjects will **not** be stored with information from IRB Protocol ID# 619037-1, through which HIPAA form is completed.
Appendix H highlights the policies related to accessing the DHIN and its security.
Personnel accessing the DHIN will be lmited to PI- Darcy Reisman and Research PT's- Tamara Wright and Henry Wright. Only subjects enrolled following approval of this amended protocol will be eligible to have medical records retrieved through the DHIN. The DHIN will provide access to the following:

- Community Health Record: Provides on-demand, patient level access to clinical and demographic information that has been collected on DHIN since 2007
- Event Notification System (ENS): Provides near real-time alerts when a participants admitted to a DHIN participating hospital, including all hospitals I Delaware, Maryland and Washington DC.
- Clinical Gateway: A real time feed of labs, radiology studies, transcription summaries and ambulator practice care summaries from all of DHINS's clinical data senders, A historical load of clinical data may also be provided

Event Notification and Clinical Gateway are panel based services so only information for patients matching the roster as provided by PROWALKS will be delivered by DHIN. DHIN restricts access to the Community Health Record (CHR) and strictly monitors the access behaviors of its users. For PROWALKS, DHIN will receive and retain the disclosures of participating patients and will review their access to the CHR on a weekly basis and will conduct a reconciliation of the records accessed by PROWALKS staff versus their patient panel to ensure that patient records are not inappropriately being accessed. Per DHIN PHI access policies, any variation will be escalated to PROWALKS executive leadership for their review and for an explanation as to the access, as there may be a valid clinical reason for the access. DHIN procedures for escalating issues will be applied in circumstances where a valid access reason does not apply to a system access.

Describe what exclusionary criteria, if any will be applied.

The specific subject inclusion and exclusion criteria are:
Inclusion Criteria: 1) Age 21-85*, 2) Chronic stroke (>6 months post stroke)*, 3) Able to walk at self-selected speed without assistance from another person (assistive devices are allowed), 4) Self-selected walking speed <1.0 m/s*, 5) Average steps/day <8,000, 6) Resting heart rate between 40-100 beats per minute*, 5) Resting blood pressure between 90/60 to 170/90*. **Exclusion Criteria:** 1) Evidence of cerebellar stroke*, 2) Other potentially disabling neurologic conditions in addition to stroke*, 3) Lower limb Botulinum toxin injection <4 months earlier, 4) Current participation in physical therapy, 5) Inability to walk outside the home prior to the stroke, 5) Coronary artery bypass graft, stent placement or myocardial infarction within past 3 months*, 6) Musculoskeletal pain that limits activity, 7) Inability to communicate with investigators, 8) score >1 on question 1b and >0 on question 1c on the NIH Stroke Scale, 9) Self-selected walking speed <0.3 m/s*.

**For recruiting participants from the Stroke Research Registry, criteria with asterisks represent data found in the Registry and may be used in search queries to more efficiently find individuals to contact who would be qualified to participate in this study.*

The inclusion and exclusion criteria are discussed at the initial screening and again on the first

testing day when the informed consent document is reviewed. Determining whether all criteria on the Inclusion and Exclusion Criteria Checklist (see Appendices) are met is based on a combination of subjects' individual responses and information from other documentation. Two inclusion criteria (walking speed between 0.3 and 1.0 m/s and steps per day <8,000) cannot be evaluated until the baseline evaluation is completed. Therefore, subjects will be withdrawn from the study if these criteria are not met following this evaluation.

Describe what (if any) conditions will result in PI termination of subject participation.

Participation in the study is voluntary. Any subject may withdraw from the study at any time without any negative consequences. In addition, the PI may terminate a subject's participation if the subject is viewed by the PI to be placing him/herself at risk. This is not expected, but could potentially occur. Similarly, the subject may be withdrawn from the study based on abnormal results identified on the symptom-limited graded exercise test.

8. **RISKS AND BENEFITS**

List all potential physical, psychological, social, financial or legal risks to subjects (risks listed here should be included on the consent form).

Participation in any physical activity or exercise has risk. These risks include but are not limited to, pain, fainting, dizziness, fatigue, nausea, shortness of breath, chest pain or angina, myocardial infarction, swelling, bruising, muscle/bone/joint soreness, joint damage, bone fracture, ligament/tendon/connective tissue damage, hospitalization, and death.

Psychological risks include possible discomfort, frustration, and/or anxiety related to difficulty with the physical testing or completion of questionnaires.

Graded exercise testing carries a low risk of myocardial infarction/cardiac arrest (1/2500; ACC/AHA) and patients will be made aware of this risk prior to testing. However, graded exercise testing is a standard procedure for diagnostic purposes, evaluation of functional capacity, and the effectiveness of both exercise and pharmacological interventions.

The risks of taking blood include pain and/or bruising where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

In your opinion, are risks listed above minimal* or more than minimal? If more than minimal, please justify why risks are reasonable in relation to anticipated direct or future benefits.

The risks of the study are not more than minimal.

What steps will be taken to minimize risks?

During treadmill walking subjects are allowed rest breaks whenever requested or deemed appropriate by the experimenter. Because participants who have sustained a stroke may be at increased cardiovascular risk, when a potential post-stroke participant contacts the team, they will be asked to provide consent to allow the investigators to contact the referring or primary physician to obtain medical opinion of fitness to participate in research. Potential participants will only be brought to the laboratory for testing once the medical opinion of fitness has been obtained. Prior to the initiation of training, all subjects will undergo a 12 lead symptom limited graded exercise test reviewed by a cardiologist. All subjects will wear a heart rate monitor during testing and training. During all treadmill walking, subjects will wear a harness connected

to an overhead support. During walking training, the Borg Scale of perceived exertion (RPE) [1] will be measured every 2 minutes and heart rate will be continuously monitored. For all training sessions, the guidelines set forth by the American College of Sports Medicine (ACSM) for individuals in phase III or IV of cardiac rehabilitation will be followed. Based on these guidelines, a session will be terminated if any of the following conditions occur:

- Drop in Systolic blood pressure of $\geq$ 10mmHg from baseline (resting for that day) despite increase in workload
- Hypertensive response with a systolic blood pressure >240 mmHg and diastolic blood pressure >110
- Presence of nervous system symptoms: ataxia, dizziness, or near syncope
- Any chest pain or angina symptoms
- Signs of poor perfusion cyanosis or pallor
- Excessive fatigue, excessive shortness of breath, leg cramps, claudication

If any of the above occurs, the subject's physician will be contacted and informed of the subject's response to the activity. Subjects can also terminate any session or training bout by stating their desire to stop.

Prior to the Graded Exercise Test (GXT), a Cardiac Guidelines Letter (Appendix E) will be sent to the subjects' MD when deemed necessary based on medical history. This will allow the MD to place any additional guidelines they would like us to follow during the GXT, training intervention/future evaluations in regards to heart rate and/or blood pressure.

Any incidents involving injury to study subjects will be presented to the Data and Safety Monitoring Board and the IRB immediately. Please see information related to the Data and Safety Monitoring Board below.

Describe any potential direct benefits to participants.
The direct benefit to the subjects participating in training could be substantial. Previous research has shown that 12 weeks of treadmill training can lead to improvements in walking speed and activity. So regardless of the effects of our specific intervention, subjects are likely to obtain some benefit of participation. This will be explained to all subjects. The methods of study will provide sensitive, objective measures of walking function and activity, which would be useful in monitoring progress, or the lack of it, across time and therapy. This will be explained to all subjects.

Describe any potential future benefits to this class of participants, others, or society.

The potential benefits of this study are that we may understand mechanisms and interventions to improve physical activity in chronic stroke survivors. The knowledge gained will provide an understanding of the optimal characteristics of rehabilitation interventions to promote functional walking recovery post stroke. Because of the potential for these results to lead to development of new approaches to rehabilitation interventions for stroke survivors that could significantly impact secondary prevention of future stroke and other conditions, the potential benefits far outweigh the minimal risks.

If there is a Data Monitoring Committee (DMC) in place for this project, please describe when and how often it meets.
There is a Data and Safety Monitoring Board (DSMB) for this study. Please see the description of the example DSMB Charter in the Appendices.

9. **COMPENSATION**
Will participants be compensated for participation? Yes.

If so, please include details.

Subjects will be paid $100.00 for participation, $25.00 after each of the evaluation time points is completed.

Participants are responsible for transportation to the study site for each visit. In some situations, if a participant cannot arrange transportation alone, transportation will be arranged for them.

10. **DATA**
Will subjects be anonymous to the researcher?

Subjects will not be anonymous to the researchers. As part of the consent process and verification of eligibility, subjects must provide their name, date of birth and other identifying information to members of the research team. However, identities will be kept confidential to the extent possible (see Confidentiality section below). De-identified data may be presented in abstract, poster, presentation, or published manuscript format.

If subjects are identifiable, will their identities be kept confidential? (If yes, please specify how)

Subject identities will be kept confidential by assigning each subject a number.

How will data be stored and kept secure (specify data storage plans for both paper and electronic files. For guidance see http://www.udel.edu/research/preparing/datastorage.html)

Encrypted electronic files that connect subject identities to their subject code will be stored in a database on a password protected UD managed server for the UD and CCHS subjects. Similar processes are in place at UPenn and IU for their subjects. These files are not shared between sites. Paper copies of consent forms for each site will be stored on-site. Paper copies of the screening form for subjects that sign the Informed Consent are also stored at each site.
All coded subject data will be collected and managed using REDCap electronic data capture tools hosted by the University of Delaware's Delaware Rehabilitation Institute. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. All sites will have access to the coded data in the REDCap database.

How long will data be stored?

All de-identified data will be stored indefinitely and may be used in future research studies.

Will data be destroyed? **X** YES ☐ NO (if yes, please specify how the data will be destroyed)
Data with identifying information will be saved until the project is complete or the data are published, whichever comes first and then the identifiable data will be destroyed. This will involve all electronic data being wiped from hard-drives and servers and all paper data being shredded. Raw de-identified data will be stored indefinitely and may be used in future related studies.

Will the data be shared with anyone outside of the research team? **X** YES NO

These data will be used by the current investigative team, and then, in compliance with NIH policy, shared with others through the NICHD DASH repository so that additional analyses can be performed. Once the primary hypotheses of the current proposal are tested, all data will be cleaned, de-identified, and be deposited in the DASH repository. To ensure that the identities of research subjects cannot be readily ascertained with the data, NICHD DASH will store only data that are without identifiers and coded. According to NICHS DASH requirements, before submitting the data to NICHD DASH, investigators must:

c. Strip the data of individually identifying information according to:
    - the standards set forth in the HHS Regulations for the Protection of Human Subjects and related guidance (which covers individually identifiable private information), and
    - the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (which covers protected health information); and

d. Assign to the de-identified data random, unique codes.

How will data be analyzed and reported?

Appropriate statistical analysis of the primary (General Linear Mixed Modeling) and exploratory (Cox Proportional Hazards Model and a Generalized Estimating Equation) outcomes will be completed under the direction of the biostatistician on the project. The results will be reported to professionals interested in research via journals and presentations.

11. **CONFIDENTIALITY**
Will participants be audiotaped, photographed or videotaped during this study?

Individual subjects may be approached and asked to be photographed or videotaped for recruitment, educational or research purposes. A photo release form will be signed by participants prior to any photographs or videotape taken. Subjects will be told that this is an optional activity and not a requirement of participation. Photographs or video will have the face covered.

How will subject identity be protected?

All participants' identifying information will be stored in a locked file cabinet (paper forms) or on password-protected computers or servers (electronic forms) and will be utilized only by investigators on the protocol who have a specific need for the identifying information. All data will be coded using a numerical system, the key to which will be maintained on a password-protected computer at UD for the UD and CCHS subjects and at UPenn and IU for their subjects. This data is maintained in the REDCap database as described above.

For medical information obtained through the DHIN:

DHIN restricts access to the Community Health Record (CHR) and strictly monitors the access behaviors of its users. For PROWALKS, DHIN will receive and retain the disclosures of participating patients and will review their access to the CHR on a weekly basis and will conduct a reconciliation of the records accessed by PROWALKS staff versus their patient panel to ensure that patient records are not inappropriately being accessed. Per DHIN PHI access policies, any variation will be escalated to PROWALKS executive leadership for their review and for an explanation as to the access, as there may be a valid clinical reason for the access. DHIN procedures for escalating issues will be applied in circumstances where a valid access reason does not apply to a system access.
Medical records obtained through the DHIN for PROWALKS subjects will **not** be stored with information from IRB Protocol ID# 619037-1, through which HIPAA form is completed.

Is there a Certificate of Confidentiality in place for this project? (If so, please provide a copy).

There is no Certificate of Confidentiality in place for this project.

12. **CONFLICT OF INTEREST**
(For information on disclosure reporting see: http://www.udel.edu/research/preparing/conflict.html)

Do you have a current conflict of interest disclosure form on file through UD Web forms? Yes
Does this project involve a potential conflict of interest*? NO

* As defined in the University of Delaware's Policies and Procedures ,a potential conflict of interest (COI) occurs when there is a divergence between an individual's private interests and his or her professional obligations, such that an independent observer might reasonably question whether the individual's professional judgment, commitment, actions, or decisions could be influenced by considerations of personal gain, financial or otherwise.

If yes, please describe the nature of the interest:

13. **CONSENT and ASSENT**

__X__ Consent forms will be used and are attached for review (see Consent Template under Forms and Templates in IRBNet)

____ Additionally, child assent forms will be used and are attached.

____ Waiver of Documentation of Consent (attach a consent script/information sheet with the signature block removed).

____ Waiver of Consent (Justify request for waiver)

14. **Other IRB Approval**

Has this protocol been submitted to any other IRBs? This study has been approved by the University of Pennsylvania's and Indiana University's IRB and that approval has been submitted as an amendment to this protocol. An Institutional Review Board Authorization Agreement has been signed between CCHS and UD.

15. **Supporting Documentation**

Please list all additional documents uploaded to IRBNet in support of this application.

Appendices which include IRBNet Protocol ID# 619037-1, entitled "Shared Pre-enrollment Process for Stroke Research Team Studies", that is referenced in this protocol, along with copies of specific clinical tests, screening questions and the inclusion/exclusion checklist for this protocol.

A separate Appendix is attached with the example DSMB charter.

REFERENCES

3. 7th ed. Philadelphia: Lippincott, Williams and Wilkines; 2006. American College Of Sports Medicine (ACSM) – Guidelines for exercise testing and prescription.
4. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970;2(2):92-8.

Summary of protocol changes

Summary of protocol changes

Approval date	Description of protocol changes
3/23/2016	Initial approval
5/1/2017	To exclude individuals who walk at <0.3m/s (due to limitations of Fitbit sensitivity); to ensure consistency in language describing training phase in protocol and consent form
10/16/2018	To add IU as an evaluation and training site
9/28/2020	To add language to consent form to reflect that while risk of COVID-19 exposure will be minimized, the risk of exposure cannot be completely eliminated

Original statistical analysis plan (excerpted from original IRB protocol (2016), NIH grant application (2014), and published protocol (2018)[1]

General data management & analysis

Encrypted electronic files that connect subject identities to their subject code will be stored in a database on a password protected server. Paper copies of consent forms for each site will be stored on-site. Paper copies of the screening form for subjects that sign the Informed Consent are also stored at each site.

The Biostatistician running analyses is blinded to group assignment. An "intent to treat" analysis will be performed. To ensure that the randomization worked, potential covariates (e.g. age, time since stroke, cognition) will be compared between groups using t-tests and $\chi 2$ tests. If a covariate is significantly different between groups, this will be an indication that the groups are not balanced and the covariate will be included in the models. The alpha is set at 0.05 for primary analyses and .01 for secondary analyses.

Aims 1 & 2 will be tested using General Linear Mixed Models (GLMM). To compare the efficacy of the FAST+SAM, FAST and SAM interventions for improving real-world walking activity in chronic stroke survivors and to determine for whom the interventions are most effective General Linear Mixed Models (GLMM) will be developed. All model assumptions will be tested (including linearity, normality, homoscedasticity, and multicollinearity). Outliers and influential cases will be screened for and removed. Violations of the assumptions will be remedied using transformations or a Generalized Linear Model. Post-hoc tests in the GLMMS will use Bonferroni adjustment and for the regression models post-hoc probing of interactions will be done using simple slopes method.[2]

For the GLMMs, the covariance structure will be chosen using nested model comparisons. The regression models also have the assumptions of homoscedasticity and multicollinearity, which will be tested using the Breusch-Pagan test, and by 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. Site differences will also be tested, and if differences exist, will be included in the model to control for them.

Power analysis & sample size

The precise increase in steps/day necessary to reduce the risk of secondary health complications and disability post-stroke is not known, however, studies in other at risk populations have shown a reduction in cardiovascular events with an increase of 2,000 steps/day.[5] Previous studies in chronic stroke, along with our data, suggest an improvement in ~1000 steps/day with fast walking training alone[3] and our recent study suggests an improvement of ~1100 steps/day with a step activity monitoring program alone.[4] Our data from the FAST+SAM intervention suggests an improvement of ~1700 steps/day in those with low steps/day at baseline and an improvement of ~250 steps/day for those in FAST with low baseline steps/day. Given this, we would consider an average improvement of ≥1700 steps/day in the FAST+SAM group worthy of further study in future clinical trials. Power calculations indicate that a total of 225 participants

are needed (75 in each of the 3 groups) in order to detect this differential increase based on baseline steps/day and intervention received with power greater than 0.90. These calculations assume equal group sizes, a moderate correlation among repeated measures of r=0.50, and a standard deviation for steps/day of 2,500.[3,4]

Expected outcomes and aim specific analysis

Aim 1. To compare the efficacy of the FAST+SAM, FAST and SAM interventions for improving real-world walking activity in chronic stroke survivors and to determine for whom the interventions are most effective. The primary measure for this Aim is number of steps per day (SPD). Data will be calculated at each time point (Baseline, post-treatment, 6 and 12 month follow-up) by finding the average number of SPD over one week.

H1.1. *All 3 interventions will improve real world walking activity immediately post-intervention.*

A GLMM will be used to evaluate changes in SPD from pre- to post-training. For this hypothesis the main effect of time will be compared, averaged across groups. If the main effect of time is significant, this research question can be answered using the marginal pairwise comparisons of SPD at baseline with post-training. If an interaction is significant, the simple main effect of time will be compared between interventions.

Aim 2. To compare the efficacy of the FAST+SAM, FAST and SAM interventions for improving walking speed, endurance and cardiorespiratory function in chronic stroke survivors and to determine for whom the interventions are most effective. The primary measure for this Aim is distance covered during the 6 minute walk test (6MWT). The secondary measures for this Aim are self-selected walking speed as measured during the 10 meter walk test (SSWS) and cardiorespiratory function as measured by peak oxygen consumption during graded exercise testing (VO_2 peak). Data will be calculated at each time point (Baseline, post-treatment, 6 and 12 month follow-up).

The same exact analyses used in **Aim 1** for all the hypotheses will be used in Aim 2 but with the outcomes of 6MWT, SSWS and VO_2 peak. Separate models will be completed for the 6 and 12 month time point.

Updates to statistical analysis plan (excerpted from final IRB protocol (2023), ClinicalTrials.gov registry (2022))

General data management & analysis - all changes from initial plan were to incorporate use of REDCap electronic databases to increase data accuracy, accessibility, and security:

Encrypted electronic files that connect subject identities to their subject code will be stored in a database on a password protected UD managed server for the UD and CCHS subjects. Similar processes are in place at UPenn and IU for their subjects. These files are not shared between sites. Paper copies of consent forms for each site will be stored on-site. Paper copies of the screening form for subjects that sign the Informed Consent are also stored at each site.

All coded subject data will be collected and managed using REDCap electronic data capture tools hosted by the University of Delaware's Delaware Rehabilitation Institute. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. All sites will have access to the coded data in the REDCap database.

Data from each evaluation session will be entered directly into the PROWALKS REDCap Clinical database. This database is designed with built in quality control checks (e.g., range checks, checking for missing data for required data points). In addition, each month the UD Research PT will examine frequency distributions of outcome variables to identify questionable data points.

Data from each training session will be entered directly into the PROWALKS REDCap Training database. This database is designed with built in quality control checks (e.g., range checks, checking for missing data for required data points). In addition, each quarter the UD Stroke Studies Coordinator will review a random sampling of data from 6 sessions at each site according to the Treatment Fidelity checklist webform.

Expected outcomes and aim specific analysis

There were no changes to expected outcomes and planned aim specific analysis between the start and end of the study.

References

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2. Aiken LS, West SG, Reno RR. *Multiple Regression: Testing and Interpreting Interactions*. SAGE; 1991.
3. Moore JL, Roth EJ, Killian C, Hornby TG. Locomotor Training Improves Daily Stepping Activity and Gait Efficiency in Individuals Poststroke Who Have Reached a “Plateau” in Recovery. *Stroke*. 2010;41(1):129-135. doi:10.1161/STROKEAHA.109.563247
4. Danks KA, Roos MA, McCoy D, Reisman DS. A step activity monitoring program improves real world walking activity post stroke. *Disability and Rehabilitation*. 2014;36(26):2233-2236. doi:10.3109/09638288.2014.903303