Clinical Algorithm for Post-Stroke Gait Training with C-Brace

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Protocol Title:	Clinical Algorithm for Post-Stroke Gait Training with C-Brace
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Population:	Human subjects (male and female), age 18 years or older, who have a diagnosis of hemiparesis or hemiplegia due to stroke, in the Houston metropolitan area.
Number of Sites:	1. TIRR Memorial Hermann
Study Duration:	2 years
Subject Duration:	8-10 weeks

GENERAL INFORMATION

Inability to walk is one of the significant challenges that affect quality of life in individuals with chronic hemiparesis. Not only is gait an important activity of daily living, it can also help minimize many of the secondary complications seen as a result of decreased mobility resulting from neurological injury, such as cardiovascular deconditioning and loss of bone mass. Assistive devices and orthoses are utilized to assist individuals with hemiparesis to regain the ability to walk, however, efficiency of walking using these devices (assisted walking) is often overlooked. Introducing an orthotic device alters the gait kinematics. The inefficiency of assisted walking could be the result of abnormal gait kinematics and kinetic patterns which are associated with outdated product design and inadequate users' ability. With advanced technology, a novel microprocessor-controlled leg orthosis system (C-Brace, Ottobock Health Care LP) has been developed to promote assisted walking with near-to-normal gait biomechanical parameters. This device, therefore, could also improve the efficiency of assisted walking.

With the advanced technology, however, little is known about which patients would receive maximal therapeutic benefits in physiology, physical function and quality of life. Therefore, the purpose of this study is to develop a clinical algorithmic-based evaluation and treatment approach for C-Brace for use by persons with hemiparesis or hemiplegia. We are mostly interested in measuring the physiological effects, specifically neuromuscular and cardiovascular parameters, and gait characteristics during walking with C-brace. We plan to identity the strongest predictors and outcome measures of walking in persons with hemiparesis or hemiplegia using the C-brace, then develop an algorithm for reliable prognosis and early subgrouping.

BACKGROUND INFORMATION

The impaired ability to walk independently is a significant consequence after neuromuscular injuries resulting in substantial limitation in mobility and performance of daily activities, thus restricting full participation and home and community re-integration [1]. Regaining the ability to walk is one of the priorities in rehabilitation in this population, however, walking efficiency and energy cost is often overlooked. The consequence of additional metabolic demand contributes to fatigue, which promotes a sedentary life style that predisposes an individual to secondary health deterioration and compromised quality of life.

Energy expenditure in walking is increased in persons with hemiparesis and hemiplegia [2]. Studies have indicated that energy cost in walking is affected by many factors such as ankle plantarflexors [3], quadriceps activity[4] and center of mass motion [5]. Therefore, walking with orthoses whose design is to compensate or correct an abnormality, could reduce energy expenditure [6] while different orthoses designs could also affect energy expenditures [7-9].

The knee-ankle foot orthosis (KAFO) is one of the most often prescribed to facilitate walking for patients with weakness of the muscles which control the knee and protect against loss of structural integrity of knee joint. Two most commonly utilized KAFOs are conventional KAFO and stance-control orthosis (SCO). The difference between these 2 orthoses is the knee control mechanism during walking: conventional KAFOs prevent knee flexion during stance and swing phase, while SCO prevent knee flexion during stance phase while allowing knee flexion during swing phase. The advantage of the SCO is it reduces the commonly observed gait compensatory strategies observed with use of conventional KAFO during swing phase to create sufficient toe clearance such as hip hiking, vaulting and circumduction and promotes improved gait kinematics[10-13]. As noted in the literature these gait compensations tend to increase energy expenditures [14-16]. Due to a reduction in gait deviations and compensations, walking with a SCO could lead to improved walking energy efficiency.

Although SCO allow users to have a more nature gait pattern, functional limitations remain. The most important limitation is the lack of dampened knee flexion in the weight bearing condition required to descend ramps and stairs and when transitioning from standing to sitting. Additionally the absence of knee flexion dampening in swing phase of the SCO orthosis results in an absence of stumble recovery, permitting a sudden loss of control and a fall. These limitations significantly affect the ability to perform daily activities not only at home but within the community as well. Recently a novel microprocessor-controlled leg orthosis system (C-Brace) has been developed to engage dampened knee flexion in the weight bearing condition to overcome the limitation from SCO[10]. Therefore, C-Brace could also promote assisted walking with near-to-normal gait biomechanical parameters and lead to a reduction of energy cost and improved quality of life.

To enhance the feasibility and success rate of interventional trials in gait training with C-brace, early identification of subgroups based on outcome predictors should be investigated. These outcome predictors could serve as inclusion and exclusion criteria for identifying subgroups of patients who may receive maximal therapeutic effects from using C-brace.

Therefore, the purpose of this study is to develop a clinical algorithmic-based evaluation and treatment approach for C-Brace for use by persons with hemiparesis or hemiplegia. We are mostly interested in measuring the physiological effects, specifically neuromuscular and cardiovascular parameters, and gait characteristics during walking with C-brace. We plan to identity the strongest predictors and outcome measures of walking in persons with hemiparesis or hemiplegia using the C-brace, then develop an algorithm for reliable prognosis and early subgrouping.

OBJECTIVES

Specific Aim 1: To quantify and compare the neuromuscular, cardiopulmonary responses and gait kinematics during walking with and without C-brace in individuals with hemiparesis or hemiplegia. We plan to recruit patients with hemiparesis or hemiplegia following stroke and include a wide range of gait impairments. It is expected that subjects will demonstrate various degree of difference in energy expenditures, neuromuscular responses, functional status and gait characteristics between walking with and without C-brace, depending on their current walking ability. We hypothesize that the changes in cardiopulmonary responses, neuromuscular responses of major lower muscle groups and gait characteristics would be greater in persons with lower functional status and severe gait impairment.

Specific Aim 2: To investigate the association between gait improvement (i.e. gait kinematics, speed and walking distance) in walking with C-Brace and baseline neuromuscular, cardiopulmonary characteristics that affect gait performance, cognition and physical function in individuals with hemiparesis or hemiplegia. We also aim to develop an algorithm to characterize and subgroup the patients who receive gait training with C-Brace. We hypothesize that the improvements observed in walking with C-Brace are related to muscle strength, range of motion, severity of spasticity and the functional status, and the degree of relations may be varied. We will then identify the key parameters and measures based on association to develop an algorithm to characterize the patients who may receive the maximal benefit of using C-Brace for walking.

STUDY DESIGN

Subjects

15 individuals with diagnosis of stroke and residual hemiparesis or hemiplegia will be grouped into one of three categories based on their walking speed at baseline. Subjects will receive 4 weeks of gait training utilizing C-Brace, 3 times per week for a total of 12 sessions. We will utilize the 10 Meter Walk Test to assess gait speed for all groups at baseline (week 0). Once training sessions are complete and subject is considered an independent experienced user (week 5) we will assess the neuromuscular and cardiopulmonary responses and gait kinematics during walking with and without C-Brace. Subjects will then continue with use of C-Brace in their daily routine in their home and community environments for 4-6 weeks. Subjects will then return for a follow up visit (week 8-10) and reassessment of neuromuscular and cardiopulmonary responses and gait kinematics during walking with and without C-Brace.

Study Population

15 individuals with hemiparesis or hemiplegia after stroke in the Houston metropolitan area. Inclusion and exclusion criteria are listed in Table 1. Participants will be screened and evaluated by study investigators and certified physical therapists. We plan to recruit individuals with a wide range of walking abilities. The walking ability will be determined by gait speed from 10 meter walk test: severe gait impairment (gait velocity <0.4 m/s, moderate gait impairment (gait speed 0.4-0.8 m/s) and mild impairment (gait speed >0.8 m/s)[17].

Table 1:

	Inclusion Criteria	Exclusion Criteria
15 subjects (5 subjects in each group) • Mild • Moderate • Severe	• Age 18 - 65 years • Diagnosis of hemiparesis or hemiplegia following stroke • Presence of abnormal walking pattern • Poor knee control during stance phase • Cognitive ability to (or care provider) manage daily charging of battery • Cognitive ability to follow commands • Hip flexor muscle strength grade 3 or greater or the ability to perform reciprocal gait using compensatory patterns • Able to operate C-brace	• Weight > 275 lbs. (Includes body weight and weight of heaviest object carried) • Less than 2° of ankle motion • Severe spasticity of the quadriceps (MAS >3) and/or uncontrolled spasticity of the quadriceps • Severe spasticity of other lower limb muscles (MAS >3) • Fixed genuvalgum exceeding 10° beyond anatomic neutral valgum • Any fixed genuvarum exceeding anatomic neutral varum. • Hip or knee flexion contractures greater than 10° • Presence of COPD • Chronic heart failure – NYHA stages 3 and 4

STUDY PROCEDURES

Fitting and Training Protocols:

Qualified participants will be fitted with the C-Brace by a certified orthotist specialist. Subjects will participate in a baseline assessment after which they will participate in training sessions for gait training from certified physical therapist(s). The length of training is 4 weeks with a total of 12 sessions (3 times per week for 4 weeks). The goal of training sessions is to progress subject's ability to walk with C-Brace over progressively more challenging environments. They will learn how to safely and independently walk with the C-Brace in the following conditions: overground walking, reciprocal slope, descending ramps and stairs and negotiation of uneven terrain. Adjustments will be made to C-Brace according to subjects ability and performance to progress them toward independence. Once subject has reached the independent/experienced user

level, they will continue to utilize the C-Brace in their home environment. Subjects will be considered as independent/experienced users when they are able to safely walk with C-Brace without a loss of balance for at least 10 meters and when they can complete this task without requiring aide from an additional assistive device or physical assistance from the therapist. Subjects will be checked off on their ability to safely ambulate in the overground environment as well as in the various conditions of slopes, ramps, steps and uneven terrain.
Once subjects are declared independent users, they will participate in a post training assessment. After training sessions have been completed, subjects will be provided with the C-Brace to use in their everyday routine for 4-6 weeks. During the home use period, subjects will continue to wear the C-Brace as they return to their normal daily activities. During this period subjects can return to see the therapist for any adjustment or re-training as needed. The daily activity will be recorded in an activity log. Subjects will return for a follow up assessment a the end of the home use training. Follow-up assessments will be scheduled at the 4 week mark, with a 2 week window allotted to allow for accommodating subject and staff schedules.
The training and assessment sessions will be conducted at UT Health Motor Recovery Laboratory at the NeuroRecovery Research Center at TIRR Memorial Hermann.

Specific Aim 1:
To quantify and compare the neuromuscular, cardiopulmonary responses and gait kinematics during walking with and without C-brace in individuals with hemiparesis or hemiplegia. We plan to recruit patients with hemiparesis or hemiplegia following stroke who present with gait impairments. It is expected that subjects will demonstrate varying degrees of energy expenditures, neuromuscular responses, functional status and gait characteristics between walking with and without C-brace, depending on their current walking ability. We hypothesize that the changes in cardiopulmonary responses, neuromuscular responses of major lower muscle groups and gait characteristics will be greater in persons with lower functional status and more severe gait impairments.

Outcome Measures:
We will measure the following parameters during gait with and without C-Brace at completion of training sessions and at follow up.

- *Timed Up and Go*: Assesses mobility, balance, walking ability, and fall risk in older adults. The test measures the time it takes the subject to perform a sit to stand from a chair with arms, walk to a mark on the ground 10 feet away and return to the seated position in the chair with arms. This test has been used in assessing stroke recovery with high reliability and validity[18].
- *10 Meter Walk Test (10MWT):* Measure of gait speed. Subjects will walk a total of 14 meters at their preferred walking speed and at a fast pace. The test measures the time it takes the subject to complete the middle 10 meters of the walk.
- *Kinematics and electromyography (EMG):* Bilateral upper and lower extremity kinematics and surface electromyography (sEMG) recordings will be collected during 10MWT. Infrared light emitting diode markers will be attached to bilateral lower extremities. The marker data will be recorded using the NDI Optotrak Certus motion capture system. Marker data will be processed using custom Matlab program to

determine lower extremity joint excursion and joint angular velocities. For EMG, we will place bipolar surface electrodes on the bilateral major leg muscles to record electromyography (1000Hz, Motion Labs 16-Channel EMG System). We will calculate the EMG amplitude and burst duration over the whole gait cycle during the 10MWT.

- *Six-minute walk test (6MWT):* This test assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance. It has good responsiveness to detect improvements in capacity to walk in stroke patients [19].
- *Metabolic expenditure during walking:* Oxygen consumption during 6MWT will be determined using a portable metabolic system. Metabolic data will be collected on a breath-by-breath basis during gait assessment. Prior to the testing, the system will be calibrated using room air and reference gas mixture. During the testing, the subject will wear the face mask at all times and will be asked to breathe normally. Subjects will also wear a heart rate monitor. The data will be synchronized with kinematic and electromyography data for further analysis. This task will be performed during walking with and without C-Brace.

Specific Aim 2:

To investigate the association between the gait improvement (i.e. gait speed and walking distance) in walking with C-Brace and baseline neuromuscular, cardiopulmonary characteristics that affects gait performance, cognition and physical function in individuals with hemiparesis or hemiplegia. We also aim to develop an algorithm to characterize the patients who may receive the maximal benefit of using C-Brace for walking. We hypothesize that the improvements observed in walking with C-Brace are related to muscle strength, range of motion, severity of spasticity and the functional status and the degree of relations may be varied. We will then identify the key parameters based on association to develop an algorithm to characterize the patients who may receive the maximal benefit of using C-Brace for walking.

Outcome Measures:

The following assessments will be measured at baseline and follow-up (without wearing C-brace):

- *Folstein Mini Mental State Examination (MMSE):* Mini Mental State Examination provides information about orientation, attention, learning, calculation, delayed recall, and construction. Several studies report acceptable validity of MMSE as a screening instrument and its relationship to functional outcome in stroke population[20].
- *Lower limb muscle strength and range of motion:* Muscle strength will be measured and quantified by using dynamometers on major bilateral lower limb muscles such as hip flexors and extensors, hip abductors and adductors, knee flexors and extensors and ankle dorsiflexors and plantarflexors. Range of motion will be measured on bilateral hip, knee and ankle joints using goniometry.
- *Fugl-Meyer Assessment – Lower Extremity and Balance*: This test evaluates and measures recovery of movement in individual post stroke. Fugl-Meyer has been used in both clinical and research settings and is one of the most widely used quantitative measures of motor impairment [21]. It uses an ordinal scale for scoring of 17 items for

the lower limb component and 7 items on the Balance component of the F-M scale (0: cannot perform; 1: can perform partially; 2: can perform fully).

- *Modified Ashworth Scale (MAS):* This test measures spasticity in patients with lesions of the Central Nervous System by testing resistance to passive movement about a joint with varying degrees of velocity. Scores range from 0-4, with 6 choices (i.e., 0, 1, 1+, 2, 3, 4), with 0 indicating normal muscle tone, and 4 indicating very high spasticity. We will measure spasticity in lower limbs.
- *Timed Up and Go (TUG) Test:* Assesses mobility, balance, walking ability, and fall risk in older adults. This test has been used in assessing stroke recovery with high reliability and validity [18]. The test measures the time it takes the subject to perform a sit to stand from a chair with arms, walk to a mark on the ground 10 feet away and return to the seated position in the chair with arms.
- *Berg Balance Scale (BBS):* A 14-item objective measure designed to assess static balance and fall risk in adult populations, with maximum summed score of 56 (higher scores represent better functional outcome). This test has been widely used to measure functional recovery in stroke patients with high reliability [22].
- *10 Meter Walk Test (10MWT):* Measure of gait speed. Subjects will walk a total of 14 meters at their preferred walking speed and at a fast pace. The test measures the time it takes the subject to complete the middle 10 meters of the walk.
- *Six-minute walk test (6MWT):* This test assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance. It has good responsiveness to detect improvements in capacity to walk in stroke patients [19].
- Orthosis Evaluation Questionnaire: consists of 72 questions as compared to 81 questions in the PEQ to be answered by the patients on a 100-mm visual analogue scale (VAS) with higher values representing better function.

Assessment Timeline

Assessment	Screening	Fitting	Baseline	C-Brace Training (3x/wk x 4wks)	Post Training	Home/ Community Use	Follow Up
	Visit 1	Visit 2, 3	Visit 4	Visit 5-16	Visit 17	4-6 weeks	Visit 18
10MWT	X		X		X		X
Trial Tool to Operate device and casting	X						
Diagnostic test orthosis and alignment assessment		X					
C-Brace fitting finalized		X					
MMSE			X				X
Muscle Strength	X		X				X
Range of Motion	X		X				X
Fugl-Meyer			X				X
MAS	X		X				X
TUG			X		X		X
BBS			X				X

6MWT			X		X		X
C-Brace Training				X			
sEMG					X		X
Gait Kinematics					X		X
Metabolic					X		X
Orthosis Evaluation Questionnaire							X

DATA and SAFETY MONITORING

We will use following strategies to prevent some expected events for this study:

1) Loss of confidentiality or privacy

Information obtained for this study will be kept private to the extent allowed by law. However, research information may be shared with the University of Texas Health Science Center at Houston Institutional Review Board (IRB), the research physician investigator, the research staff and others who are responsible for ensuring compliance with laws and regulations related to research.

The study will be performed at at UT Health Motor Recovery Laboratory at the TIRR NeuroRecovery Research Center. All data collection records will be locked in the Study Coordinator's office in a locked file cabinet. Energy consumption, sEMG and motion capture files will be saved to the research computer using de-identified data. All computers are password protected and therefore, only authorized persons have the access to the electronic files saved in computers and will adhere to TIRR MEMORIAL HERMANN standards.

2) Loss of saved electronic data after a computer crash

All original data will be maintained on paper data collection forms. De-identified data may be entered into computer for data analysis. A standard procedure of electronic file backup is established and enforced by the PI. All file backups are routinely performed in the local hard drive. However, if there are other unanticipated problems which occur during and after data collection: the original paper version of the data will be maintained in the locked file cabinet.

3) Muscular soreness or fatigue

Borg Rating of Perceived Exertion *Scale* (Borg) will be administrated periodically throughout the intervention sessions. Subject will be provided with rest period as needed, in particular if BORG rating ≥ 17.

4) Loss of balance or fall from testing

All subjects will be able to independently ambulate. The addition of the C-Brace will provide increased stability for the subject when standing and performing transitional movements. Therefore, the use of the C-Brace will reduce the risk of falls for subjects. There is a training period to allow the subject to become familiar with the C-Brace. One research team member will remain next to the subject throughout the training session and during all testing procedures to prevent loss of balance or fall whether sitting or standing. As subjects advance their skills and progress to independent users their fall risk will continue to decrease.

If a fall or significant loss of balance occurs, one staff physician will be notified immediately. All adverse events will be reported per CPHS protocol.

5) Possible skin irritation

Local irritation, bruising, swelling, or temporary discomfort following wearing of the C-Brace may occur. Prior to donning the C-Brace subject's skin will be inspected by a licensed Physical Therapist for baseline, and compared after doffing. Any differences will be recorded and followed up with the study physician accordingly. All adverse events will be reported per CPHS protocol.

STATISTICS

Aim 1:

The effects of C-Brace on dependent variables will be analyzed using separate 2-factor (group x condition) analyses of variance (ANOVA) with repeated measures on the walking condition (walking with and without C-Brace). The model will first test for the interaction to determine if 3 groups (mild, moderate and severe) respond similarly across time. In the event of a significant interaction ($p<.05$) we will test for differences between among groups at each point in time (post hoc Tukey).

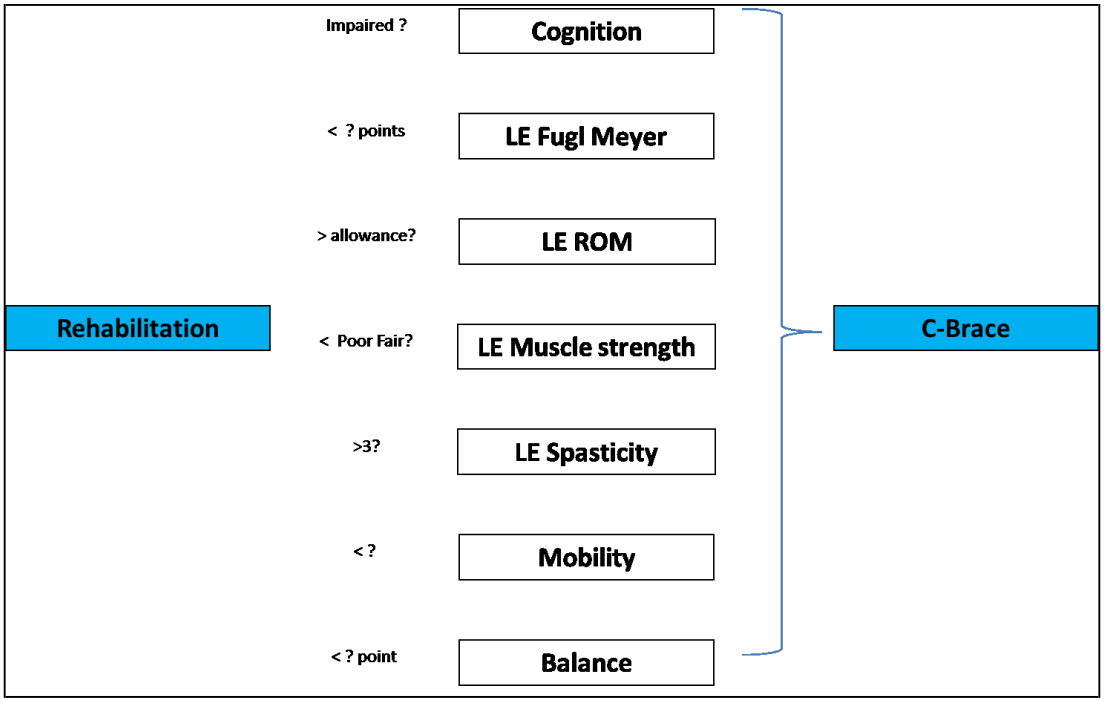
Aim 2:

Pearson product-moment correlation coefficients will be used to examine relationships among muscle strength, range of motion, spasticity, scores in Fugl-Meyer assessment and Berg Balance Scale. Hierarchical regression analyses will then be conducted to determine whether changes in gait speed and distance could be predicted on the basis of muscle strength, range of motion, spasticity, scores in Fugl-Meyer assessment and Berg Balance Scale. The order of entry will be based on presumed causal priority and to allow removal of confounding variables.

Clinical Algorithm

Algorithm and the order of the elements (Figure 1, in the middle) will be developed based on the results in the regression analysis. Figure shows the design of the algorithm. The characteristics are those we hypothesize could have impacts on the effects of using C-brace on walking performance. If the subject meets the minimal criteria of these elements, we could suggest the subject would receive the maximal benefits of using C-Brace. Larger scale study is needed to determine the minimal criteria for each element.

Figure 1



ETHICS

The study will be performed under the prevue and in accordance with the rules set by the Committee for the Protection of Human Subjects (UT IRB). Potential subjects will be identified by physiatrists working in the outpatient clinic and/or on the inpatient wards at The Institute for Rehabilitation and Research (TIRR) Memorial Hermann. Once identified, the potential subjects will be approached and asked if they wish to discuss a study utilizing a new orthosis (C-Brace) to help people with hemiplegia after stroke achieve a better gait pattern (better walking). It will also be explained that choosing not to inquire further about the study will in no way jeopardize the relationship with anyone at TIRR or in the Memorial Hermann system. Once the potential subject agrees he/she will be introduced to either the Principal Investigator or the Study Coordinator. Once the potential subject agrees to discuss the study, the individual and anyone that the potential subject wishes to accompany him/her will go into a private room to discuss the contents of the consent form with either the Principal Investigator or the Study Coordinator.

We will also post flyers in the TIRR Memorial Hermann outpatient clinics as well as online at the TIRR Memorial Hermann's Neurorecovery Research Center website.

After the consent is reviewed in its entirety, and after allowing ample time for questions, either the Principal Investigator or the Study Coordinator will give the potential subject time to discuss the study with whomever the potential subject cares to discuss the study with. If the subject agrees to enroll in the study, the Study Coordinator or Principal Investigator will review the informed consent form with the subject in its entirety.

DATA HANDLING and KEEPING

The subject's name and demographic information will be collected prior to testing. Each subject will be assigned an identification number which will be used from this point forward. All measurements will be stored according to the identification number. The Study Coordinator's locked office contains a locked file cabinet in which research materials are kept. All computers are password protected and only authorized persons have the access to the electronic files saved in computers. Paper data will be stored in the Study Coordinator's office in a locked file cabinet. Access to the file cabinet will be given to the Primary Investigator and authorized team members. All electronic data stored on the hard drive of the desktop machine will be password protected and available only to the authorized research team members. Identifiable data will be stored for 5 years after the study is completed. Stored files will be deleted from the portable hard drive after 5 years as well. Identifiable data will be shredded at the end of 5 years after the completion of the study.

QUALITY CONTROL and ASSURANCE

To ensure research integrity, standard written procedures for all tests will be established by the Principle Investigator and the Study Coordinator who will then assess each team member's competence for research conduction on a regular basis. Therefore, the testing protocol will be consistent throughout the entire data collection for this study.

PUBLICATION PLAN

The results of this study will be used for presentation at national conferences and publications in peer-reviewed journals. The publications will be provided without cost to the study participants.

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