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NYU Langone Health

A pilot, single-site study to assess the effect of exoskeletal support on motor control strategies in individuals with stroke

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NYULMC Study Number:	s23-00842
Funding Sponsor:	Dr. Heidi Schambra Resource Allocation Program
IDE Number:	N/A
Regulatory Sponsor:	Heidi Schambra, MD
Study Product:	Shoulder exoskeleton for gravity compensation (“exoskeleton”)
Study Product Provider:	Custom device, built by PI
ClinicalTrials.gov Number	N/A

Initial version: 7 July 2023
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Amended:
Amended:
Amended:

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation (“ICH”) Guideline for Good Clinical Practice (“GCP”) (sometimes referred to as “ICH-GCP” or “E6”) will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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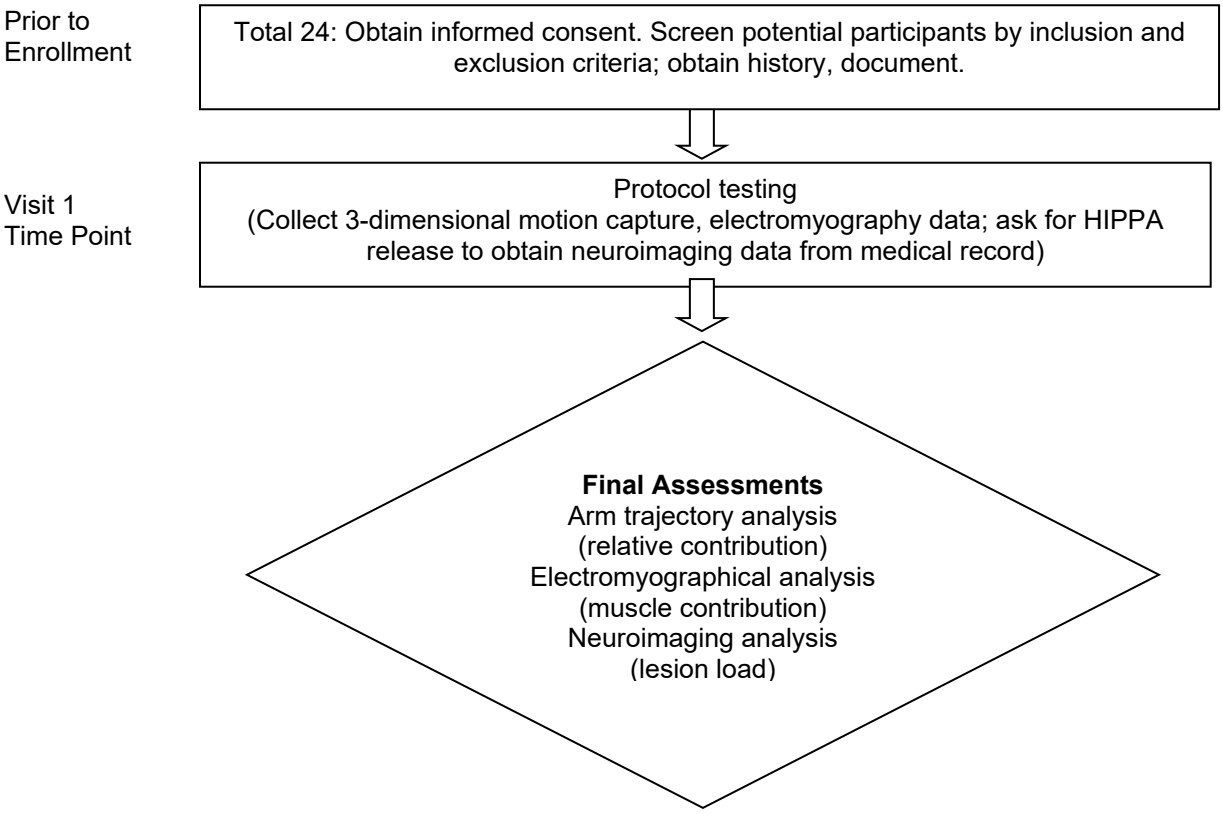
List of Abbreviations

AE	Adverse Event/Adverse Experience
CIMT	Constraint-induced movement therapy
VR	Virtual reality
OFCT	Optimal feedback control theory
EMG	Electromyography
MRI	Magnetic resonance imaging
DWI	Diffusion weighted image
UE-FM	Upper-extremity Fugl-Meyer Assessment
CST	Corticospinal tract
RC	Relative contribution
MC	Muscle contribution
PHI	Protected health information
PII	Personal identifying information
NICHD	National Institute of Child Health and Human Development

Protocol Summary

Title	A pilot proof of concept, single site study to assess the effect of exoskeletal support on motor control strategies in individuals with stroke
Short Title	Exoskeletal support in stroke
Brief Summary	This interventional study will measure motor performance, including 3D movement analysis and muscle activity, in response to exoskeleton assistance. The cohort design will compare stroke patients to healthy controls. Data collection will be conducted in a single, 2-hour session. We will also access stroke patients' brain MRIs that were obtained as standard of care during acute admission for stroke.
Phase	Pilot
Objectives	The primary objective is to examine in a VR environment whether additional gravity compensation from exoskeletal support will improve bimanual coordination in stroke patients. A second primary objective is to determine intervention effects on muscle control processes underlying bimanual coordination. As a secondary objective, we aim to correlate these measures with measures of stroke lesion characteristics.
Methodology	Cohort design
Endpoint	The primary endpoints will be a 2% increase in RC and a 5% decrease in MC. The secondary endpoint will be a significant relationship between the change in MC (% decrease in MC) and CSTLL with an R^2 value greater than 0.4
Study Duration	12 months
Participant Duration	One, 2-hour session
Duration of IP administration	Approximate 15 minutes
Population	24 participants; 12 with history of stroke more than 6-months prior to enrollment, 12 healthy age- and gender-matched controls. Males and females 18-years old and older from with and without diagnosis of stroke.
Study Site	Single-center (NYULMC)
Number of participants	24
Description of Study Agent/Procedure	We use a custom designed and built exoskeleton device that applies a torque to both shoulders. Torque values do not exceed 50% of the torque due to gravity. The device is mounted to a testing chair and attached to the participant using Velcro straps.
Reference Therapy	N/A
Key Procedures	No clinical procedures are required
Statistical Analysis	Inferential group statistics (t-test, mixed design ANOVA); correlation, linear regression

Schematic of Study Design



1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Stroke is the 5th leading cause of death in the United States, and nearly 8 million Americans report it as their primary cause of disability (Virani et al., 2021). Of particular concern is that 38% of stroke survivors report major difficulty in using their impaired arm (Duncan et al., 2003). Recent advances in rehabilitation sciences have identified learned non use as a potential mechanism by which hemiparetic stroke survivors limit use of their impaired limb (Taub et al., 2006). Therapy programs such as constraint-induced movement therapy (CIMT) have been developed to counter learned non use; however, these therapies have failed to show sustained benefits likely due to time, expense, and the lack of bimanual training tasks (Kwakkel et al., 2015; Wolf et al., 2006). Therefore, there exists a critical need for new stroke therapies that are cost effective and allow for robust bimanual coordination.

Our innovative approach uses virtual reality (VR), in conjunction with custom-built exoskeletons, to provide stroke patients with the task and environmental factors needed to increase use of their paretic limb. Therefore, the long-term goal of this work is to develop device-based rehabilitative platforms that promote impaired arm use in chronic stroke. VR based applications have emerged as new treatment approaches in stroke rehabilitation settings over the last ten years. One of the most important advantages that a VR system can provide is that it allows researcher to create visual environments which surround the user to in a way that cannot be possible in physical reality. For example, by encouraging shared control of a virtual object, it is possible to couple the hands to promote increased use of the paretic limb during reaching (Diedrichsen, 2007).

We also use a custom-built exoskeleton to provide assistance to the impaired arm in stroke patients. Specifically, the exoskeleton provides gravity compensation, a process where the force of gravity is canceled out, fully or partially, by the exoskeleton mechanics (Chen et al., 2019). Exoskeletons have been used for research purposes for decades, and emerging clinical applications are at the forefront of motor impairment rehabilitation sciences (Collins et al., 2015; Gueye et al., 2021; Keeling et al., 2021).

Our current understanding of the combination of VR and exoskeleton modalities to improve arm function in stroke is lacking. The specific aim of this study is to determine if gravity compensation, via exoskeleton loading, can increase impaired arm use in stroke participants during a VR reaching task. This study will advance the field of stroke rehabilitation by demonstrating the feasibility of shared-control reaching tasks in VR as a potential therapeutic solution for upper extremity stroke impairment.

Recently, we completed a feasibility study in which we show our protocol is safe and effective in altering limb coordination in 12 healthy control subjects (Brunfeldt et al., 2022). Moreover, we completed a study in 14 chronic stroke survivors and found they tolerated the procedures without incident (Brunfeldt et al., 2023, *in review*). Our study in stroke survivors additionally shows that integrity of the corticospinal tract is associated with motor performance in our task. This paves the way for mechanistic approaches to neuroimaging biomarker studies (Cassidy et al., 2018; Stinear, 2017; Zhu et al., 2010).

2.2 Name and Description of the Investigational Agent

The investigational agent is a custom designed and built exoskeleton device. The device, detailed in section 6, is not commercially available, is not registered with the FDA and does not have an IND or IDE status.

The device is a wearable, non-implantable exoskeleton designed to provide gravity compensation. Gravity compensation is defined as the application of torque to the shoulder that counteracts the torque due to gravity. That is, the torque vs. angle profile is equal and opposite to that of gravity. For the purposes of this study, we will only use a 50% gravity compensation (i.e., the magnitude of torque is 50% that of gravity). The purpose of the device is to assist stroke participants while they reach for virtual objects in a VR environment.

2.2.1 Preclinical Data

The study investigator, Alexander Brunfeldt, PhD, recently completed a study at the MedStar Health Research Institute (STUDY00004671) using these devices on 14 stroke participants. We did not find a significant change in RC or MC (primary endpoints) at the group level. However, we did find individual differences in outcomes that could be explained by lesion characteristics. Specifically, stroke participants with more overlap between the lesion and the corticospinal tract had a smaller change in muscle activity during exoskeletal support compared to no exoskeletal support (Brunfeldt et al., *in review*). We did not observe any adverse event.

2.2.2 Clinical Data to Date

N/A. No clinical data to date.

2.2.3 Dose Rationale

The 50% gravity compensation level was selected based on previous research in healthy controls (Brunfeldt et al., 2022) and our recently completed study (Brunfeldt et al., *in review*). In both studies, 50% was sufficient to change arm coordination and was well tolerated by participants.

2.3 Rationale

This study is aimed at evaluating whether additional gravity compensation using an exoskeleton device will improve bimanual coordination chronic stroke survivors. The study addresses key limitations such as allowing participants to use both arms to perform activities of daily living, opposed to the traditional impaired-only approach in CIMT. Our study also allows for the identification of neuromuscular mechanisms of arm control in stroke. Specifically, we hypothesize that exoskeleton loading will increase reaching distance of the impaired arm while simultaneously decreasing the amount of muscle activity required. Our initial studies show individual differences in each participant's responsiveness to our device. Therefore, we hypothesize that there is a relationship between motor performance and lesion characteristics such as size and location of the stroke infarct. Our cohort design allows us to compare motor performance between stroke survivors and age-matched healthy controls. This allows us to test specific predictions from the optimal feedback control theory (OFCT) approach to movement (Todorov & Jordan, 2002). Specifically, we can identify each participant's sensitivity to different forms of sensory feedback (e.g., vision vs. proprioception). This information is critical in developing personalized device-based rehabilitation protocols. There are no specific problems associated with using healthy controls as a control group. We will take every precaution to ensure demographic balancing between groups.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Potential risks of the exoskeleton include arm fatigue and soft-tissue (e.g., muscle, skin) discomfort. Fatigue is not greater than minimal risk because the arm movements will mimic reaching for an object on a shelf at eye level. No more than 54 reaches will be made in any single testing block, and these reaches are self-paced. Soft-tissue discomfort may arise from the exoskeleton applying a force to the arm. Discomfort poses no greater than minimal risk because the participant will only wear the device for approximately 5 minutes during the data collection phase. Also, the magnitude of force applied to the arm is no more than 50% of that due to gravity. The upper arm weighs approximately 5.77% of body weight ((Plagenhoef et al., 1983). For example, a 150 lbs. person would receiving a loading amount to counter 8.65 lbs. of force. The exoskeleton device will be worn during all testing blocks, however, the load is only applied during the 'loading phase' which lasts approximately 5 minutes.

It is anticipated that participants may be inconvenienced by the amount of time necessary to complete the study and may experience fatigue because of completing required reaching tasks in the VR system. Very rarely, participants may experience short-term dizziness or headache because of using the head mounted display of the VR system. Participants will be given ample time for practice and rest, and they may take a break and/or discontinue the study at any time.

To limit the risks associated with VR headset and exoskeleton use, we will provide the participant with breaks every 5-minutes. Also, all reaches will be self-paced. Participants will be verbally instructed that they may request unscheduled breaks during the data collection blocks. These unscheduled breaks will not affect data integrity. We also use padding and elastic gauze on the arms to reduce pressure and abrasion risk.

There is a potential risk of breach of confidentiality. To mitigate this, procedures will be carried out in a laboratory space on the NYULMC campus. We are requesting personal health information from the patient's medical record. To mitigate this, access will only be granted to named persons on this protocol; data will be stored on TrialMaster.

2.4.2 Known Potential Benefits

There is no direct benefit to individual study participants.

Information gained in this study will inform the next generation of rehabilitative therapies for chronic stroke survivors. The potential benefits to the stroke community outweigh the potential risks to participants due to participants' exposure to no more than minimal risk.

This study aims to explore the optimal control strategies implemented during reaching. As learned nonuse represents a maladaptive compensation in response to upper extremity dysfunction, targeted rehabilitative therapies that rebalance the effort required for reaching may provide clinicians with additional tools for treating chronic stroke. While this study cannot address the probability, magnitude, or duration of potential benefits, we expect a future iteration of these procedures could help the nearly 8 million stroke survivors living with disability.

3 Objectives and Purpose

3.1 Primary Objective

To identify the effects of gravity compensation from exoskeletal support on bimanual coordination in stroke participants during a reaching task in VR. Specifically, we will determine if gravity compensation can increase the reaching displacement of the impaired arm relative to the non-impaired arm. We will compare stroke participant performance to healthy controls to determine if stroke influences an individual's kinematic responsiveness to exoskeletal support.

To determine the effects of gravity compensation from exoskeletal support on bilateral muscle activity in stroke participants. Specifically, we will determine if gravity compensation can reduce the required muscle activity needed to perform the VR reaching task. We will compare stroke and healthy control participant muscle activity to determine if stroke influences an individual's neuromuscular responsiveness to exoskeletal support.

3.2 Secondary Objectives

To establish corticospinal tract lesion load as a correlate of kinematic and neuromuscular responsiveness to exoskeletal support. We do this by associating the change in RC (or MC) with the variance in overlap between the lesion and the corticospinal tract (CST lesion load) using clinical standard of care MRI scans.

4 Study Design and Endpoints

4.1 Description of Study Design

In this study, we aim to use a virtual reality reaching task with exoskeletons to increase use of the impaired limb in stroke survivors. For all participants, they will complete 3 blocks of 54 trials in a single session. Block 1 is a baseline phase where subjects will perform reaches without any loads applied via the exoskeleton devices. Block 2 is the intervention block where bilateral exoskeletons apply gravity assistance to the impaired arm for stroke survivors and gravity resistance to the non-impaired arm. In healthy controls, assistance is applied to the non-dominant arm and resistance is applied to the dominant arm. Block 3 is a retention block, where tested procedures are identical to block 1.

Virtual Reality Task

In each block, the subject will be asked to sit on a chair, wear the Oculus headset, and hold a touch controller in each hand to reach through a target displayed in the VR system (Figure 1). Subjects can see two avatar's hands, representing their own hands movements, in the VR environment. Each experimental block includes 54 trials. In each trial, the subject is asked to put his/her hands on his/her laps as a starting position. After the start position is achieved, a target cube will show up in the VR environment and the subject will use both hands to reach the cube. A cursor, located at the midpoint of the hands, will be used to 'hit' the target cube during each trial. The same horizontal locations of the targets used in a previous VR study will be used (Wang et al., 2021). Target locations will span the workspace from approximately ±15 degrees located at shoulder and eye level. This distribution is chosen to simulate reaches typically made in activities of daily living. The sequence of target locations will be randomized. Subjects' hand movements will be confined to a quadrant and the radius will be scaled to each subject's arm length, within the subject's comfortable range of motion. Subjects can move at their own comfortable speed.

Figure 1: Oculus Rift headset and touch controller bundle

Exoskeleton device

Subjects will be asked to wear an exoskeleton device (Figure 2). This exoskeleton was designed and constructed by our lab to provide either gravity assistance or gravity resistance. Gravity assistance will be applied to the impaired arm of stroke patients and to the non-dominant arm of healthy controls. Gravity resistance will be applied to the non-impaired arm of stroke patients and to the dominant arm of healthy controls. Assistance/resistance levels are adjusted to provide a 50% change in arm weight based on the shoulder torque required to abduct the upper extremity. For example, for a 150lb person, the 50% resistance configuration would simulate adding a weight, W, equal to 2.33 lbs. at the wrist (0.5*T = 0.5*BW*0.0533*0.447 = W*0.7687) (Plagenhoef et al., 1983). More detail on the exoskeleton device is in Section 6 Study Agent.

Electromyography

Muscle activity will be measured using surface electromyography (EMG). Non-invasive electrodes (Biometrics Ltd, UK) will be applied to the skin of the subject over several muscles of interest including anterior deltoid (bilaterally), triceps (bilaterally) and the short head of the biceps brachii (bilaterally). Maximum voluntary contraction will be assessed 3 times for both forward shoulder abduction and elbow flexion. Participants will be asked to produce a maximum force for 3-5 seconds while experimenters measure muscle activity. Sixty seconds of rest will be provided between MVC assessments. These data will be used to normalize outcome measures. EMG muscle activity will be recorded throughout each session.

Figure 2: Exoskeleton in gravity resistance configuration

Neuroimaging

Finally, we will obtain neuroimaging data from the participant's electronic medical record (EMR). The Study Investigator will obtain written consent (see Consent Form) to access the participant's EMR, where they will download the diffusion weighted image (DWI) scan obtained through standard of care at NYULMC. **No new imaging will be required**. Downloaded DWI images will have personal identifying information removed. The DWI will be analyzed in the ITK-SNAP (http://www.itksnap.org/pmwiki/pmwiki.php). We use this software to manually trace the lesion to obtain a lesion mask. This lesion mask is then standardized to the Montreal Neurological Institute stereotaxic space (Mazziotta et al., 2001) using the SPM12 mapping software (Karl Friston, https://www.fil.ion.ucl.ac.uk/spm/). We then determine the overlap between the lesion mask and the CST (Zhu et al., 2010).

Study Timeline

The study will take place on the NYULMC campus in a single, 2-hour session.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoints will be a 2% increase in RC and a 5% decrease in MC. These values are taken from (Brunfeldt et al., 2022).

4.2.2 Secondary Study Endpoints

The secondary endpoint will be a significant relationship between the change in MC (% decrease in MC) and CSTLL with an R^2 value greater than 0.4 (Brunfeldt et al., *in review*).

4.2.3 Exploratory Endpoints

N/A

5 Recruitment

Starting immediately after IRB approval and lasting for approximately 12 months, subjects will be acquired by convenience sampling. The Study Investigator (Alexander Brunfeldt, PhD) will recruit subjects via a participant registry maintained by the Principal Investigator (Heidi Schambra, MD). The participant registry includes both survivors of stroke and healthy control participants. The registry is maintained by the PI to "develop a resource that researchers can use to recruit healthy individuals and patients with stroke in IRB-approved studies conducted by the Mobilis Laboratory" (s18-00959). We may also recruit participants through word of mouth from other studies conducted in the PI's laboratory.

The patient's affected hand will be examined to determine if the patient's impairment satisfies inclusion/exclusion criteria in one of the NYULMC treatment rooms allocated for research activities. After it is determined that the subject is eligible to participate in the study, the consent process will proceed. During the consenting process, all subjects will have the purpose of the experiment, the complete procedure, and any potential risks involved in participation in the study explained to them by the investigators. Participants in the stroke group will receive a one-time $50 check following their participation in our study. Healthy control participants will receive a one-time $25 check. The reason for this difference in value is the potential for increased burden on stroke patients regarding transportation (i.e., some are not medically cleared to operate a motor vehicle) and care due to their impairment.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Healthy controls

1. Having obtained the age of 18 years
2. Neurologically healthy (i.e., no history of: traumatic brain injury, peripheral neuropathy, seizures, etc.)
3. Strongly right-handed according to at least 80% score on the Edinburgh Handedness Inventory (Oldfield, 1971; Veale, 2013). The use of right-handed participants is a common feature in this field of study. This is due to the slight differences in arm control between left- and right-handed individuals (Sainburg & Kalakanis, 2000).
4. Ability to give informed consent

Survivors of stroke

1. Having obtained the age of 18 years
2. have a diagnosis of stroke more than six months prior to entry into the study;
3. have the ability to reach, unsupported, to approximately 70% of arm length
4. ability to give informed consent

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

All participants

1. have any conditions that limit their capability of using a Head Mounted Display (HMD) for a VR environment or cooperate with the protocol.
2. have any orthopedic injuries to the upper extremities.
3. Have neurological injuries other than stroke.
4. Have excessive pain in any joint of either arm that could limit the ability to cooperate with the protocols.
5. Visuospatial neglect
6. Apraxia
7. Global inattention
8. Legal blindness

5.3 Vulnerable Subjects

This study does not propose to enroll vulnerable subjects.

5.3.1 Adults without Capacity to Consent

This study will not recruit individuals with impaired consent capacity. We expect 0% of the contacted stroke participants to lack the capacity to consent. These patients will have already consented in the past; therefore, a formal capacity assessment is not warranted. Informal judgment that prospective participants have the capacity to consent will be made through routine interactions with the individual during the consent process. Capacity will be determined by the Study Investigator to assess the prospective participant's verbal understanding of the protocol including the purpose, objectives, potential risks and benefits of participation. We will explicitly ask them to recollect

the purpose, risks, and benefits after explaining and prior their signing the consent form. We will not consent or enroll any individual suspected of diminished capacity to consent.

5.3.2 Assessment of Capacity

Assessment of capacity will be done by the Study Investigator, Alexander Brunfeldt, PhD. The assessors are study team members that are identified in Research Navigator.

The individual performing the assessment and/or monitoring ongoing capacity will perform the assessment through routine interaction with the prospective participant during the consent process.

The results of the capacity assessment will not be placed in the subject's medical record. Results will not be placed in the participant's medical record because we are not performing a formal capacity assessment.

Prospective subjects will be informed of the results of the capacity assessment after it's conducted. If an individual is found not to have the capacity to consent, the assessor will explain this to the individual. The assessor will provide the necessary resources and referrals for further care and evaluation.

5.3.3 Surrogate Consent

N/A. Enrolled participants will possess capacity and therefore not require a surrogate.

5.3.4 Ongoing Assessment of Capacity

At each study visit, subjects will have direct interaction with the Study Investigator, Alexander Brunfeldt, PhD or study team members identified in Research Navigator. If assessors have any concerns about the subject's capacity, a capacity assessment will be conducted as described above. Subjects who lose capacity will be withdrawn from the study. Subjects who appear to be unduly distressed will be withdrawn from the study.

5.4 Duration of Study Participation

Participants will be asked to participate in a single, 2-hour session. This includes enrollment, screening, and completion of the protocol requirements.

5.5 Total Number of Participants

Recruitment will end when approximately 24 participants are enrolled. It is expected that approximately 30 participants will be enrolled in order to produce 24 evaluable participants.

5.6 Participant Withdrawal or Termination

5.6.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant fails to adhere to protocol requirements
- Subject withdraws consent
- Subject experiences excessive fatigue or discomfort

Abrupt withdrawal or termination from study will not affect participant safety or clinical management.

5.6.2 Handling of Participant Withdrawals or Termination

The proposed study does not seek to obtain follow-up data. As such, withdrawn or terminated participants will not be contacted for further data collection for the given protocol. Replacement of withdrawn or terminated participants will follow with standard recruitment and retention policies outlined in 5.4 Strategies for Recruitment and Retention.

5.7 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the NYU IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

6 Study Device

6.1 Study Device

We designed a bilateral exoskeleton to apply a torque to the shoulder joint when participants reach for targets in a virtual reality environment. We use rubber bands to apply force to the upper arm about an axis of rotation pointing through the glenohumeral joint. The mechanics are designed to ensure the torque profile generated by the exoskeleton matches the torque profile generated by the force due to gravity through a range of motion from neutral (anatomical position) to 120 degrees of forward flexion. Our exoskeletons have two operating modes. In the gravity assistance mode, the torque vector points opposite (180 degrees) that of the gravity torque vector. In the gravity resistance mode, the torque vector points in the same direction (0 degrees) as the gravity torque vector. That is, torque profiles are equal to 50% in magnitude, but opposite in direction to that of gravity. We apply gravity assistance to the impaired arm (non-dominant for healthy controls) and gravity resistance to the non-impaired arm of our stroke participants.

This study will use two devices: an Oculus Rift Headset and a custom-built exoskeleton.

Oculus Rift headset: The Oculus Rift is a commercially-available virtual reality headset manufactured and sold by Meta Inc. It is used to present the visual environment in which participants perform the reaching task.
This is not a medical device in the context of the study since we are not evaluating the safety or efficacy of this device in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.

In addition the device is not intended to affect the structure or any function of the body.

Exoskeleton Device: The exoskeleton device was designed and constructed by the study investigator, Alexander Brunfeldt, PhD. The bilateral device is used to support the impaired arm (non-dominant in healthy controls) against gravity while simultaneously resisting movement of the non-impaired arm of stroke participants. We consider the device to be a non-significant risk device as it meets the criteria for an abbreviated IDE. Please see the “Appendix: Investigational Device” in the Devices section for justification.

6.1.1 Acquisition

The exoskeleton device was designed and constructed by the study investigator, Alexander Brunfeldt, PhD. This device is stored in a locked room on the NYULMC campus. The device will only be used by the study team for this study and no other study.

6.1.2 Formulation, Appearance, Packaging, and Labeling

We designed the exoskeleton in SolidWorks (Dassault Systems, Aachen, Germany). A schematic of the shoulder piece is shown in Figure 3. Planar pieces (e.g., arm piece) were laser cut from 1/4" acrylic. Volumetric pieces (e.g., arm holster) were 3D printed using ABS plastic.

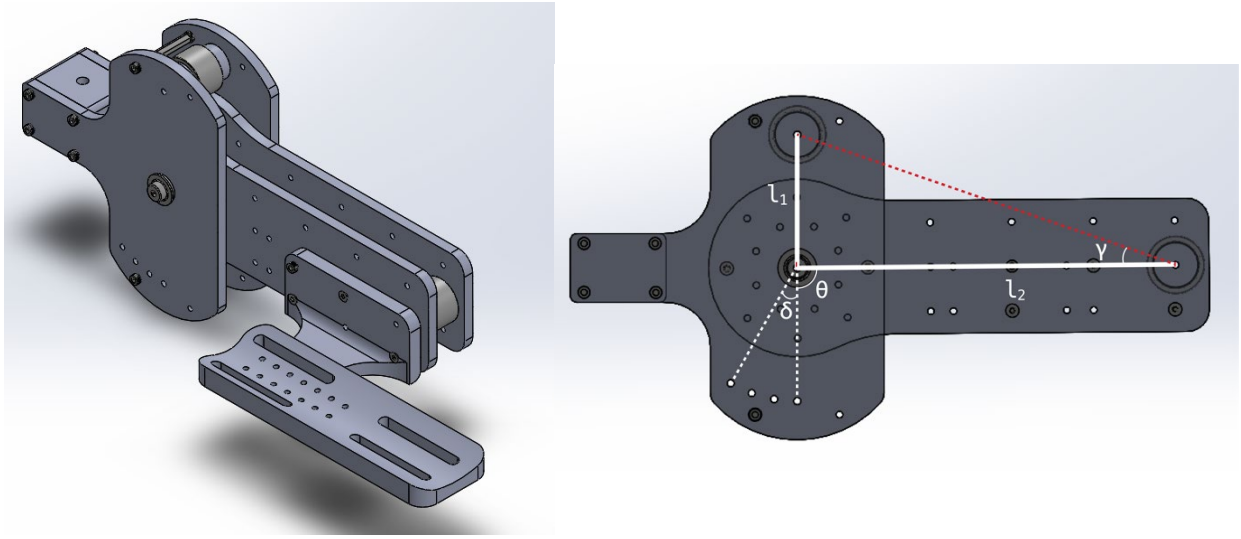

Figure 3: Left shoulder exoskeleton device in assist mode. *Left panel:* Isometric view of the exoskeleton. *Right panel:* Sagittal view of the exoskeleton with arm holster removed.

The exoskeleton device is mounted to the participant testing chair using a custom-built frame. The frame was constructed from 1" T-slotted framing rails, which allowed us to raise and lower the exoskeleton device so that its axis of rotation aligned with the glenohumeral joint. We placed the participant's arm into the holster piece (Figure 3, left panel) and secured it using two Velcro straps. Rubber bands were looped around two needle-roller bearings to reduce friction. These rubber bands produced a force directed along a vector pointing from the distal needle bearing towards the proximal one, indicated by the red dashed line in Figure 3, right panel. In the configuration shown in Figure 3, the rubber bands produced a torque directed against gravity (assist mode). We could move the proximal needle bearing to the inferior portion of the device to produce a torque in the same direction as gravity (resist mode). The device is investigational and not commercially marketed.

6.1.3 Product Storage and Stability

The device will be stored at the offices of the study team in a locked testing room. The device does no expire.

6.1.4 Preparation

N/A. The agent is not an IDS.

6.1.5 Dosing and Administration

Based on the mechanics of the device, derived in our previous study (Brunfeldt et al., *in review*), we determined the number of rubber bands needed to produce 50% gravity compensation:

The final calculations yielded the following linear relationships
$\tau_{assist} = 1.089N_{5"x5/8"} + 0.16N_{7"x1/8"} - 0.13\ (Nm)$
and
$\tau_{resist} = 0.722N_{7"x5/8"} + 0.17N_{7"x1/8"} + 0.7\ (Nm)$

where N is the number of rubber bands with subscript indicating length and width (i.e., $N_{5"x5/8"}$ is the number of 5”x5/8” rubber bands). For example, the rubber band configuration for an individual with arm length of ~0.57m and weight ~75kg:

Assist mode: 5x5”x5/8” + 2x7”x1/8” = 5.64 Nm, which is approximately 50.7% of the torque due to gravity of her fully outstretched arm.
Resist mode: 6x7”x5/8” + 3x7”x1/8” = 5.54 Nm, which is approximately 49.8% of the torque due to gravity of her fully outstretched arm.

6.1.6 Route of Administration

The study device will be attached to the participant using Velcro straps. The device be supported by a metal frame attached to a chair in which the participant is seated. The device setup will be performed by the study investigator, Alexander Brunfeldt, PhD.

6.1.7 Starting Dose and Dose Escalation Schedule

Starting dose is 50% gravity compensation. There is no escalation.

6.1.8 Dose Adjustments/Modifications/Delays

There will be no dose adjustment or modification.

6.1.9 Duration of Therapy

Study participants will complete all requirements within the single, 2-hour session. They will wear the device for no more than 15 minutes.

6.1.10 Tracking of Dose

Torque levels will be set by the study investigator on a per-participant basis, equal to 50% of the torque due to gravity.

6.1.11 Device Specific Considerations

- Device size. Approximately 1 meter, fully extended
- Device model. N/A. Custom, non-commercial device.
- Device settings and programming. 50% gravity compensation.
- Duration of implant or exposure. No more than 15 minutes.
- Frequency of exposure. One.

6.2 Study Agent Accountability Procedures

N/A. The study agent is not a pharmaceutical or investigational drug agent.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Both stroke participants and healthy controls will participate in a single session. Both groups will undergo the same protocol with two exceptions. Stroke participants will be asked to provide permission to review their medical records; they will also perform the Fugl-Meyer Assessment if no recent score has been obtained.

Task	Stroke	Controls
Consent	X	X
Inclusion/exclusion	X	X
Demographic Information	X	X
Edinburgh Handedness Inventory – Short From	X	X

Fugl-Meyer Assessment (as needed)	X	
Virtual Reality Task (with EMG and exoskeleton)	X	X
Access & download neuroimaging	X	

7.1.1 Study Specific Procedures

- *Medical history:* stroke information (date, location, hemorrhagic vs. ischemic)
- *Medication history:* None
- *Radiographic or other imaging assessments.* No new assessments will be acquired, but we will obtain standard of care imaging from hospital admission.
- *Biological specimen collection and laboratory evaluations. None*
- *A discussion of if the results of any study specific procedures (e.g., radiographic or other imaging or laboratory evaluations) will be provided to participant.* None.
- *Counseling procedures.* None
- *Assessment of study agent adherence.* N/A. No investigational agent
- *Administration of questionnaires or other instruments for patient-reported outcomes, such as a daily diary.* If participants do not have an Edinburgh Handedness Survey, one will be given to them. See Appendix.

7.1.2 Other Assays or Procedures

Fugl-Meyer Assessment and Edinburgh Handedness Inventory Questionnaire data will be used to screen for eligibility. The MOBILIS (Dr. Schambra's) laboratory registry contains these data (s17-00447, s18-00959).

7.2 Study Schedule

The study consists of a single, 2-hour session. It is typical for participants to finish within 90-150 minutes. All procedures are conducted ONLY for research purposes. No procedures will supplant standard of care. No procedures will interfere with standard of care.

Participants will be contacted via phone call or text message, during which the Study Investigator will provide the prospective participant with a synopsis of the purpose and objectives of the research, a brief description of the protocol, and any potential risks and benefits. The prospective participant will be verbally informed that participation is completely voluntary. Upon verbal agreement of the prospective participant, the Study Investigator will schedule the single visit at the participant's earliest convenience, usually within one-week of initial contact.

The Study Investigator will also ask verbal consent to view the prospective participant's medical records. We inform the participant that no data will be downloaded or collected about the medical record, only that we use this to screen those with acute MRI imaging and to obtain the Fugl-Meyer assessment score (see Section 6.1).

The single session will begin with the informed consent process. After obtaining consent, we will gather information about the participant (e.g., age, height, weight, etc.; see Section 10). We then administer the Edinburgh Handedness Inventory Short Form (Oldfield, 1971; Veale, 2013). We then let the participant practice with the VR headset; we attach the EMG sensors; we attach the exoskeletons. We then start data collection on the VR task protocol. Participants finish their participation with maximum voluntary contraction measurement. We then provide the participant with the appropriate stipend amount and ask them if they have any questions/concerns about their participation.

7.2.1 Screening

Screening Visit (Day -28 to -1)

- Contact potential participant via phone, text, SendSafe, or MyChart. Provide verbal information about purpose, objectives, procedures, any potential risks and benefits to participation
- Ask permission to access medical records. Study Investigator will screen for those participants with acute DWI neuroimaging in the NYULMC system. No data will be collected or downloaded at this point in the study. This is only for screening purposes.

- We will also determine if the participant has a recent Fugl-Meyer assessment (within 12 months). If no Fugl-Meyer score is available, the Study Investigator will administer the assessment during the visit (~15 minutes).

- Instruct participants that they are to wear or bring a short-sleeved shirt to the visit. This is so we can attach the EMG leads to the participant's arms.

7.2.2 Enrollment/Baseline

As this is a single-session observational study, enrollment, baseline, and testing is planned in the same visit.

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain and document consent from participant on study consent form.
- Verify inclusion/exclusion criteria.
- Obtain demographic information.
- Edinburgh handedness survey
- Administer full protocol.

8 Assessment of Safety

8.1 Specification of Safety Parameters

No study endpoint are considered safety parameters. No safety parameters will be recorded. The dose of 50% gravity compensation has been used in our previous work with no reports of adverse events (Brunfeldt et al., 2022, Brunfeldt et al., *in review*).

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

8.2.3 Expectedness

Alexander Brunfeldt, PhD will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product

(assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation should be recorded and reported immediately.

8.4.2 Serious Adverse Event Reporting

Investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others.

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.4.3 Unanticipated Problem Reporting

In the event of a UP, the study investigators will send a UP report to the IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within one week of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within one week of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one week of the IR's receipt of the report of the problem from the investigator.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study investigators will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.6 Reporting Procedures – Notifying the FDA

The following describes the IDE safety reporting requirements by timeline for reporting and associated type of event:

- Within 5 working days (via written report)
  - Protocol deviation to protect the life of the subject in emergency
  - Withdrawal of IRB approval
  - Lack of informed consent
- Within 10 working days (via telephone or facsimile report)

Any study event that is:

- associated with the use of the study device, and
- unanticipated, regardless of the seriousness of the event.

Additional reporting requirements
Sponsors are also required to identify in safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events will be in a narrative format. As such, the minimum information to be supplied is noted above at the beginning of section this section. The contact information for submitting safety reports is noted below:

Reports will be sent via the FDA.gov website using the FDA Form 3500

8.7 Study Halting Rules

No halting rules will be used. The study poses no more than minimal risk to participants. Participants are free to withdraw at any time for any reason.

8.8 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (DSMP). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

<u>Data Safety Monitoring Plan</u>
Safety oversight will be under the direction of the study PI, Heidi Schambra, MD and the study investigator, Alexander Brunfeldt, PhD. The DSMP members will meet twice, once at the 6-month time point and again at the 12 month time point, to assess safety data on each arm of the study. Safety will be assessed by quantifying the number, percentage, magnitude, and frequency of:

- Headache
- Dizziness
- Arm soft-tissue discomfort
- Complaints (non-specific to anticipated risks)
- Breaches of confidentiality

There are no halting rules for this study. A summary of the outcomes of these safety reviews along with accumulated adverse events and deviations will be submitted to the IRB as part of an annual progress report at the time of the Continuing Review submission.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s):

- The NYU Human Research Protection Program may monitor the progress of the study. Monitoring will occur at the HRP's discretion on a random basis at any frequency it deems necessary to ensure compliance and study safety.
- Independent audits will not be conducted to ensure monitoring practices are performed consistently across all participating sites. This is a single-site study.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

There will not be a formal SAP.

10.2 Statistical Hypotheses

Primary endpoint. Exoskeletal support will increase RC in stroke participants. Paired t-test comparing RC from baseline to loading blocks.

Primary endpoint. Exoskeletal support will decrease MC in stroke participants. Paired t-test comparing MC from baseline to loading blocks.

Secondary endpoint. There will be an association between change in RC (or MC) and CST lesion load. Independent linear regressions (RC vs. CSTLL and MC vs. CSTLL).

Secondary endpoint. RC values in stroke participants will be less than RC values in healthy controls during baseline blocks (t-test). MC values in stroke participants will be greater than MC values in healthy controls during baseline blocks (t-test).

10.3 Analysis Datasets

All participants will be included the analysis dataset. The analysis dataset will include all relevant variables:
Outcome variables

- Relative contribution (RC)
- Muscle contribution (MC)
- CST lesion load (CSTLL)

Independent variables

- Loading (via exoskeleton)

Demographic variables

- Age
- Height
- Weight
- Time since stroke (stroke only)
- Lesion type (hemorrhagic vs. ischemic)
- Arm length
- Handedness
- Fugl-Meyer score (stroke only)

10.4 Description of Statistical Methods

10.4.1 General Approach

This study is a repeated measures cohort design. Two groups of participants (stroke, healthy control) will perform a reaching task with and without an exoskeleton device. Primary endpoint measures will be compared within-subject to assess the effects of exoskeleton loading on coordination (kinematic: RC and muscular: MC). A between-subjects analysis will be performed to assess differences in arm control between stroke and healthy control participants.

- For descriptive statistics, we will use ranges, means, and standard deviation as appropriate. For example individual ages will be reported and further summarized with mean and standard deviation.
- For inferential statistics, we will perform two-tailed paired- and unpaired t-tests and ANOVA where appropriate. Statistical significance will be assessed at the Type-I error less than $p = 0.05$ level. See Section 10.4.2.
- Covariates will not be pre-specified
- Statistical test assumptions will be analyzed following data collection. Appropriate adjustments (e.g., normality) will be performed, such as transformation or the use of non-parametric tests.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

Primary study objective (change in RC, MC)

- Two-way ANOVAs on RC are conducted with within-subjects factor block (baseline, loading, retention) and between-subjects factor cohort (healthy, stroke). Three-way ANOVAs on MC are performed with within-subjects factors block and muscle (deltoid, biceps) and between-subjects factor cohort.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary study objective (Motor performance vs. CST lesion load)

- We first perform linear regressions to assess the relationship between lesion load and Upper Extremity Fugl-Meyer (UE-FM). Coefficient of determination (R2) values ranging from 0.2 to 0.7 have been previously reported (Cassidy et al., 2018; Feng et al., 2015; Lin et al., 2019; Zhu et al., 2010).
- We regress lesion load into the change in RC (ΔRC), change in MC (ΔMC), and tradeoff slope. Any motor performance measures that fail to achieve R^2 values greater than 0.2 when regressed to CST lesion load will be discarded from further analysis.

10.4.4 Safety Analyses

The study does not contain safety endpoints. Adverse events will be coded using the following identifying table:

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

10.4.5 Adherence and Retention Analyses

Adherence to the protocol will be assessed, calculated, and verified by the study investigator, Alexander Brunfeldt, PhD. Dr. Brunfeldt is under full control of the administration of the intervention. The intervention dose has been verified in previous work to be safe for participants (Brunfeldt et al., in review). In the event of a participant's wish to discontinue the protocol before study endpoint, that individual's data will be removed from analysis.

10.4.6 Baseline Descriptive Statistics

Participants will be selected from the MOBILIS lab registry. We will ensure that both groups (stroke vs. healthy control) will have the same number (frequency analysis) of men and women. We will also age match across groups. We may perform a t-test on age to ensure parity between groups.

10.4.7 Planned Interim Analysis

N/A. Single session study

10.4.7.1 Safety Review

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant fails to adhere to protocol requirements
- Subject withdraws consent
- Subject experiences excessive fatigue or discomfort

Abrupt withdrawal or termination from study will not affect participant safety or clinical management.

10.5 Sample Size

Study Hypotheses: (Primary study objective)

- A power analysis using a moderate effect size (Cohen's f = 0.25 – 0.3) on MC, power of 0.8, and significance level of 0.05 suggests a total sample of 20-28 participants (10-14 per group). This is consistent with previous work using shared cursor tasks in stroke (Brunfeldt et al., 2022; Ranganathan et al., 2019).

Study Hypotheses: (Secondary study objective)

- An *a priori* power analysis with an effect size f^2 = 0.7-0.9, a power of 1-β = 0.8 and error probability α = 0.05 results in a target sample size of 12-14 participants. The estimated effect size was directly calculated from a Partial R^2 = 0.4648 using data from a feasibility study currently in preparation for publication. This R^2 value was taken from the relationship between lesion load and the change in MC from baseline to loading conditions.

Assumptions used in calculations:

- Assumed normal distribution, or corrected to normal distribution (e.g., via log-transform)
- We plan to enroll 30 participants, with between 6-8 stroke participants not meeting inclusion/exclusion criteria. The final N = 12 endpoint accounts for these dropouts.
- Data from withdrawn participants will not be included in the final dataset. Only those who complete all procedures will be included in the final analyses.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

Enrollment will be initiated by the study investigator, Alexander Brunfeldt, PhD. Dr. Brunfeldt will contact participants via phone, SendSafe Secure email, or MyChart. Stroke participants will be contacted if they meet the inclusion criteria and assigned to the stroke group. Healthy control participants will be recruited on a rolling basis to match the age and gender of the stroke group. There is no randomization, blinding, or masking proposed.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol:

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research

participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on TrialMaster. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived with the Study Investigator and Principal Investigator.

Data will not be shared with additional investigators or third parties without prior approval from the participant. We will conform to any institutional, state, or federal auditors need to access data upon reasonable request.

13.5 Future Use of Data

Data collected for this study will be analyzed and stored at NYULMC. After the study is completed, the de-identified, archived data will be transmitted to and stored at NYIULMC controlled cloud services (e.g., Google Drive), under the supervision of Heidi Schambra, MD, for use by other researchers including those outside of the study.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research. When the study is completed, access to study data and/or samples will be provided through the NYIULMC controlled cloud services.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data are collected from four sources:

- Six degree of freedom hand position. The 3-dimensional position and 3-dimensional rotation of both Oculus Rift touch controllers. Type: electronic
- 6-channel electromyography (EMG). EMG muscle activity of the biceps, triceps, and anterior deltoid (bilaterally). Type: electgronic
- Demographic and characteristic data such as age, sex, height, weight, handedness, time since stroke, and arm length. Type: paper
- Medical records will be used to determine the type (ischemic vs. hemorrhagic) and location (cortical, subcortical, left vs. right) of stroke. Medical records will also be used to access the subject's acute DWI imaging. Type: electronic

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster. a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.1.1 Data Collection Tools – Mobile Health Technology

Products and Device

The commercial product(s) made by Meta, LLC (Oculus VR headset) and Biometrics Ltd (EMG system) permit recoding of kinematic and muscular activity information and will be used to collect study data. These devices will be used in accord with the Terms of Service and/or the End User License Agreements (EULA) provided by the product or device vendor. These products and devices will only be used to collect study data with IRB approval and if the subject has agreed to all applicable Terms of Service.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed

or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee’s responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study is funded through Dr. Heidi Schambra's resource allocation funds.

15.2 Costs to the Participant

There are no direct, personal costs to the participant other than the participant's time. Study costs will be covered by Dr. Schambra's RAP package.

15.3 Participant Reimbursements or Payments

Participants in the stroke group will receive a one-time $50 check following their participation in our study. Healthy control participants will receive a one-time $25 check. The reason for this difference in value is the potential for increased burden on stroke patients regarding transportation (i.e., some are not medically cleared to operate a motor vehicle) and care due to their impairment.

The value of reimbursements is set at a level that should not induce or coerce participation. Disbursement of the checks will be made at the completion of the testing session. If the participant wishes to withdraw from the study prematurely, they will still receive the check.

16 Study Administration

16.1 Study Leadership

The study leadership consists of Heidi Schambra, MD (PI) and Alexander Brunfeldt, PhD (Study Investigator). Dr. Schambra will oversee all aspects of the protocol and ensure that proper rules, regulations, and procedures are followed. Dr. Brunfeldt will conduct all aspects of the protocol, including consenting, data collection and analysis, preparation of oral and written communications (posters, manuscripts, etc.). The study leadership will meet biweekly.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the NICHD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

The following list of attachments are included in the IRB Uploads

- Aa-Conset_VR_EXO_Imaging
- Ab-VR-EXO_Imaging_recruitment flyer
- Ac-VR_EXO_Imaging_Datasheet
- Ad-Edinburgh Handedness Inventory - Short Form
- Ae-Phone_Script_Verbal_Screening

20 Schedule of Events

Activity	**Visit Name** [Day 1]
Study team procedures	
Consent	X
Inclusion/exclusion	X
Demographic Information	X
Edinburgh Handedness Inventory – Short From	X
Fugl-Meyer Assessment (stroke only; as needed)	X
Virtual Reality Task (with EMG and exoskeleton)	X
Access & download neuroimaging	X