Chief Science Officer

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PROTOCOL TITLE: Evaluation of the Safety and Efficacy of a Lower Extremity BiOMOTUM Exoskeleton in the Pediatric Population with Cerebral Palsy

PRINCIPAL INVESTIGATOR:

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VERSION DATE:

06/01/2022

STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	BiOMOTUM RAAD/BiOMOTUM SPARK/other similarly updated BiOMOTUM model
IND / IDE / HDE #	
Indicate Special Population(s)	☒ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	30
Funding Source	National Institutes of Health (NIH)
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☒ Yes ☐ No

OBJECTIVES:

Research Objectives

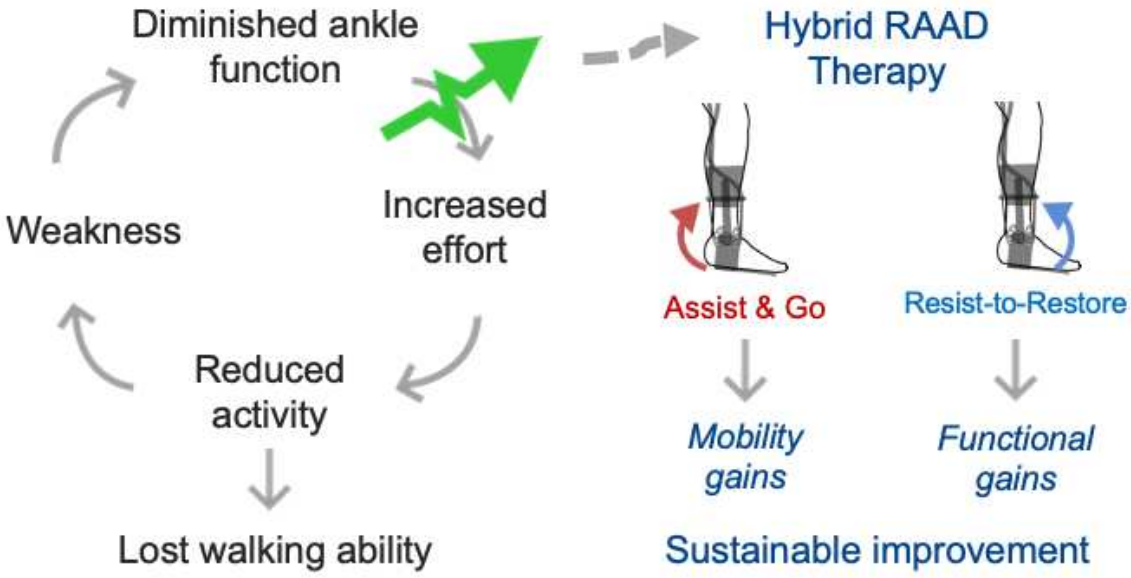
- Determine the effects of tri-weekly BiOMOTUM RAAD/BiOMOTUM SPARK/other similarly updated BiOMOTUM model resistance training on mobility-related and neuromuscular outcomes for two delivery modes:

1. Resistance training always under physical therapy (PT) supervision (optimal delivery mode)
2. Resistance training with one PT-supervised session and two parent-supervised sessions per week to mimic how the resistance intervention would be realistically implemented during daily life.

- Evaluate the safety of the BiOMOTUM RAAD/BiOMOTUM SPARK/other similarly updated BiOMOTUM device in providing gait training intervention for persons with mobility impairments secondary to cerebral palsy through incidence of device related adverse events including serious adverse events and falls.
- Explore the participant characteristics (e.g. age, gender, GMFCS level, walking speed, spasticity rating) that are associated with the greatest improvement in outcomes following each intervention.

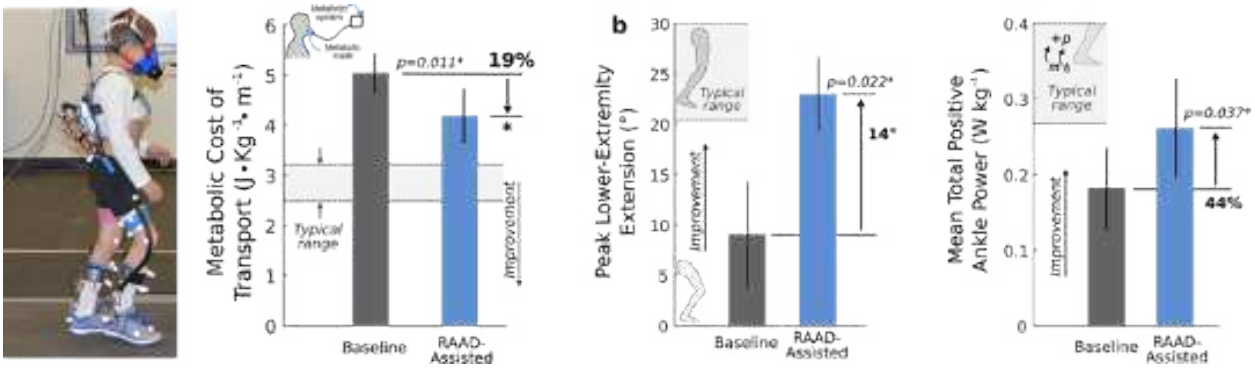
BACKGROUND:

Clinical need – Children with cerebral palsy (CP) frequently experience a downward trend of reduced physical activity and worsening gait, leading to a permanent decline or loss in ambulatory ability (Fig. 1) [7]. For children with CP, walking is drastically more energetically expensive than for their typically developing peers [8]. Experts have called for new ways to elevate activity levels in children with movement disorders [2], [9]. The ankle joint plays a critical role during walking, acting to stabilize, support, and propel the body [10]. Activation of the ankle plantar flexor muscles is reduced, less modulated, and often accompanied by co-activation of the antagonist dorsiflexor muscles in a majority of individuals with spastic cerebral palsy (CP) [11]. Reduced ankle performance during walking in children with CP is suggested as a primary contributor to the observed gait dysfunction [12]. Ankle plantar-flexors of children with CP produce 50% less positive joint work than in typical gait [1], resulting in a reliance on more proximally located muscles for forward progression [13]. These muscle activation characteristics likely contribute directly or indirectly to reduced energy exchange [14], elevated metabolic cost of transport [15], and lower levels of physical activity [16] in this patient population. Evidence suggests that addressing or augmenting the neuromuscular deficits at the ankle may allow children with CP to engage in greater amounts of habitual physical, which would likely have many additional physical and mental health benefits [17], [18].



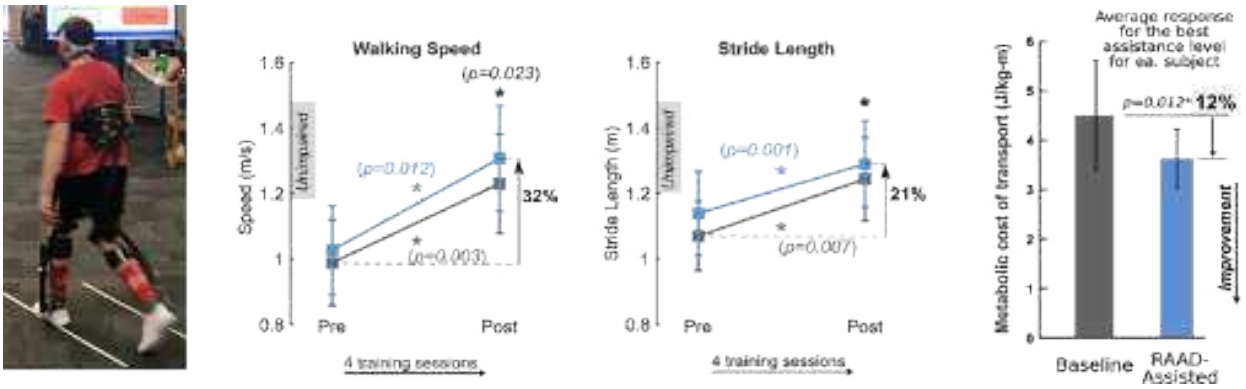
Preliminary Data

RAAD/SPARK Assistance – We have demonstrated improvements walking outcomes following treadmill and overground assistance-mode interventions. In our first **treadmill** study [3], [6], five participants with CP (ages between 5 and 30 years) practiced walking on an instrumented treadmill at self-selected speeds with powered plantar-flexion assistance. Participants exhibited a **19% reduction** ($p < 0.05$) in net metabolic cost of transport (J kg-1 m-1) on average during treadmill walking with assistance compared to their normal (baseline) walkin condition. We also found that, compared to baseline, participants had reduced crouch by 14.4 ± 4° ($p < 0.05$)
across the lower-extremity and increased in positive ankle power by 43.6 ± 7.4 % ($p < 0.05$), and decrease positive hip power, by 29.2 ± 6.0% ($p < 0.01$) All of these changes are biomechanically favorable.

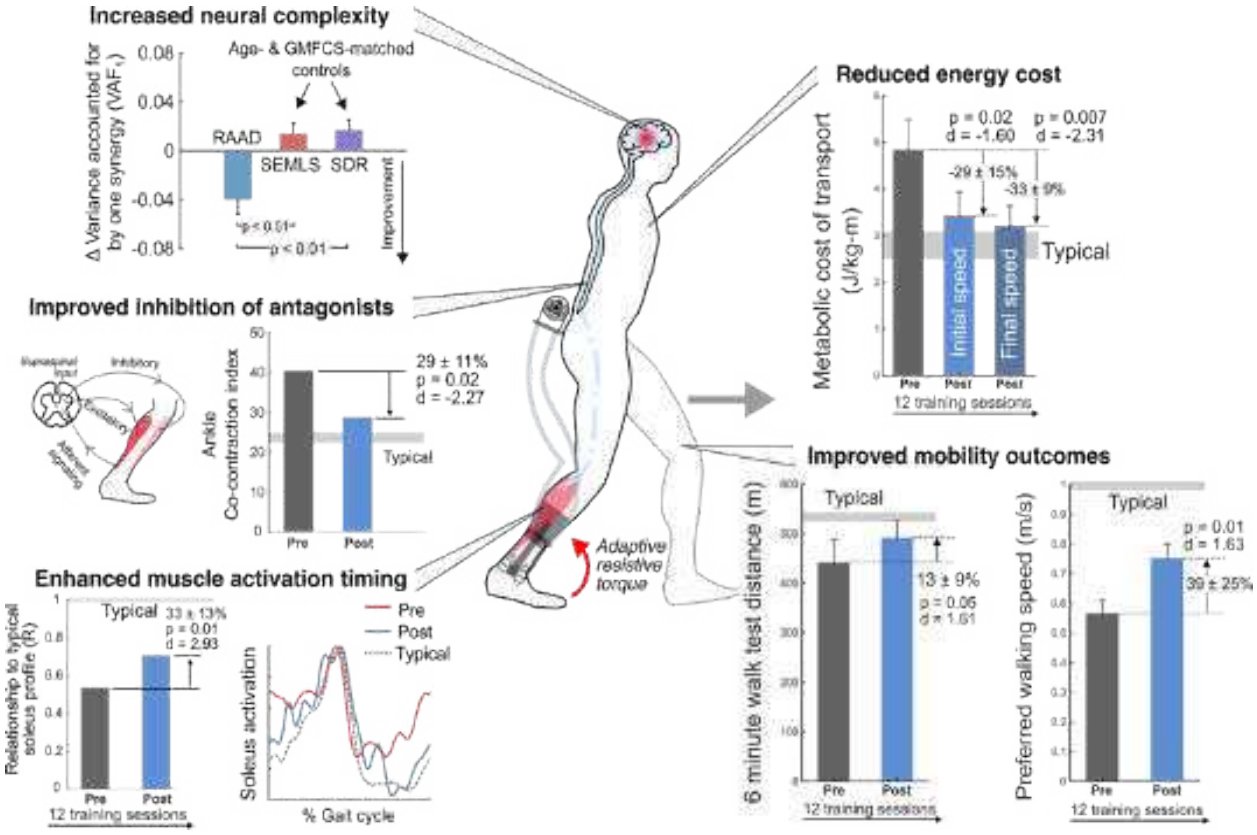


Pilot over-ground training study: 6 individuals with CP (GMFCS I-III (I:3, II:1, III:2), ages between 7 and 31 years) completed four consecutive-day over-ground training sessions (89 ± 16 minutes of assisted walking) and received pre- and post-training assessments [4]. Following training, walking speed increased 0.24 m/s ($p = 0.006$) and stride length increased 0.15 m ($p =$

0.002) during unassisted walking, while walking speed increased 0.28 m/s (p = 0.023) and stride length increased 0.17 m (p = 0.013) during RAAD-assisted walking. RAAD training improved stride-to-stride repeatability of soleus and vastus lateralis muscle activation by up to 49%, while the amount of integrated stance-phase muscle activity was similar across visits and conditions. Relative to baseline, post-training walking with the exoskeleton resulted in a soleus activity pattern that was 39% more similar to the typical pattern from unimpaired individuals (p < 0.001). In a head-to-head comparison to shod walking on the final visit, the optimized assistance level for each participant resulted in a **12.0 ± 4.0%** (p=0.012) reduction in metabolic cost of transport. To the best of our knowledge, this is the first reported improvement in over-ground walking efficiency for individuals with gait impairments.



RAAD/SPARK Resistance Precision Ankle Therapy Pilot Study (4-weeks, n = 6) – Participants completed ten, 20-minute training sessions over the course of 4 weeks with progressively increasing levels of resistance. Precision resistance led to significantly improved (reduced) stance-phase ankle co-contraction (29 ± 13%, p = 0.04), a more normal plantar flexor muscle activation profile (30 ± 15%, p = 0.02). We also observed an increase in complexity of neural control of walking after training (5 ± 3%, p = 0.04), an improvement that was significantly greater than those seen with age- and GMFCS-matched controls who had single event multi-level surgery (SEMLS) or selective dorsal rhizotomies (SDR) (p < 0.01 for both). These improvements in neuromuscular control led to a more mechanically-efficient gait pattern (58 ± 34%, p < 0.05), improved metabolic cost of transport (29 ± 15%, p < 0.05), and enhanced performance on tests of functional mobility (11 ± 9%, p = 0.04) and walking endurance (13 ± 9%, p = 0.05). The rate at which wearable adaptive resistance re-training elicited improved function was 3 – 6 times greater than what has been reported previously for gait training interventions [20], [21].



STUDY ENDPOINTS:

Primary Endpoints

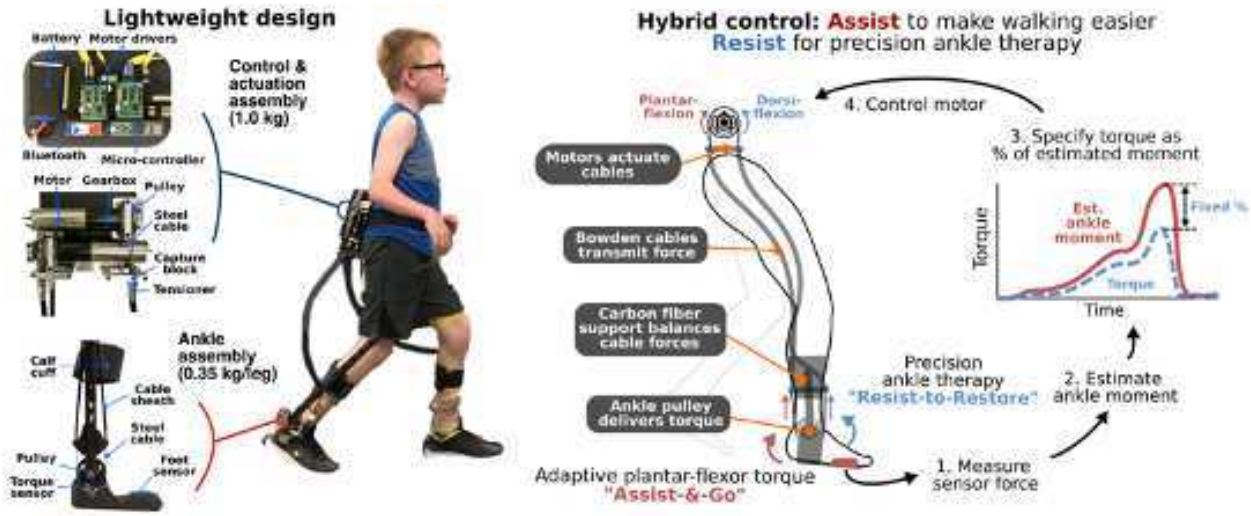
- Safety of the RAAD/SPARK for providing gait training interventions to address mobility impairments for children with cerebral palsy. This will be assessed by the number of device related adverse events including serious adverse events and falls throughout the duration of the study, including follow-up.
- Improvement in self-selected gait speed, as measured by the 10 Meter Walk Test without the device, following 12 sessions of training with the BiOMOTUM RAAD in resistance mode, as compared to baseline.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

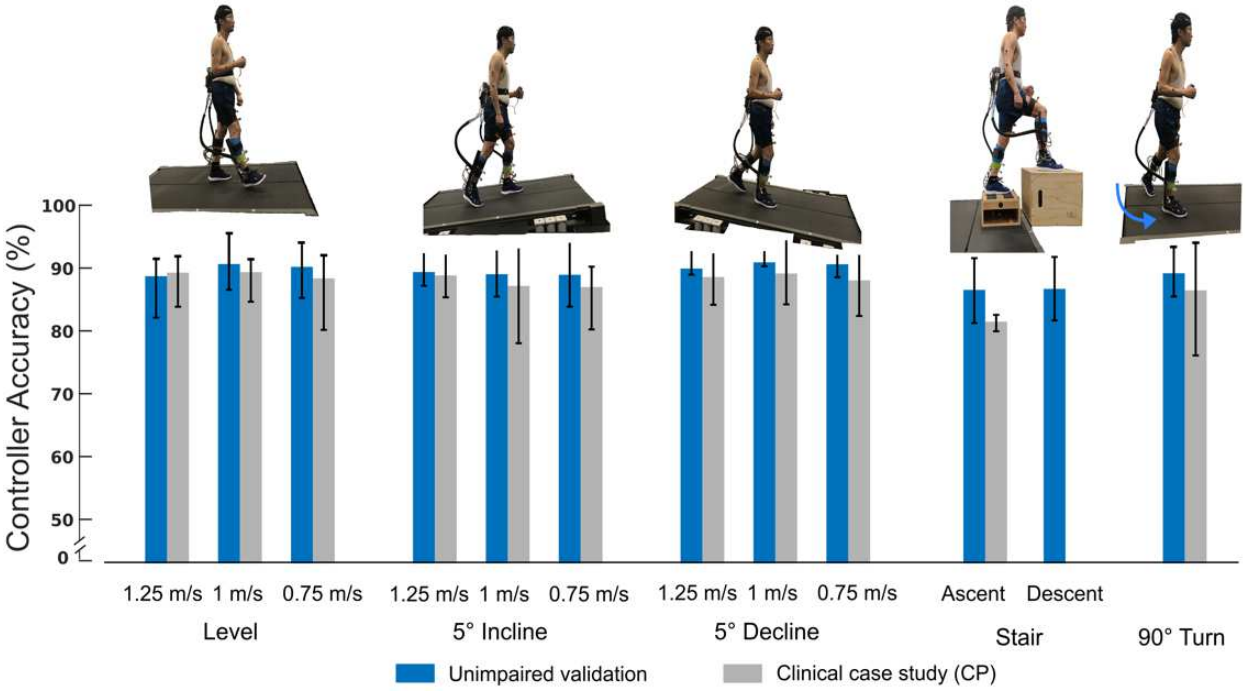
The RAAD/SPARK solution – The BiOMOTUM RAAD/SPARK is an intelligent, powered ankle device designed to increase independence, mobility, and deliver gait training to children with movement disorders, such as CP (details reported in [4], [6], [19]). Unique features of the RAAD include:

• Lightweight (<1.5kg, 70% resides around the waist) and grows with the child.
• *"Assist-and-Go"* – All-terrain mobility assistance (both stance and swing phase assistance [18])
• *"Resist-to-Restore"* – Precision ankle neuro-rehabilitation resistance therapy for long-term gains [5]
• Battery powered and cloud-connected – Tracks improvement and compliance; creates virtual community
• Simple, inexpensive, and fast to manufacture – Minimizes material and assembly costs
• Design that accommodates differences in anatomy (e.g. adjustable waist straps, cable lengths)

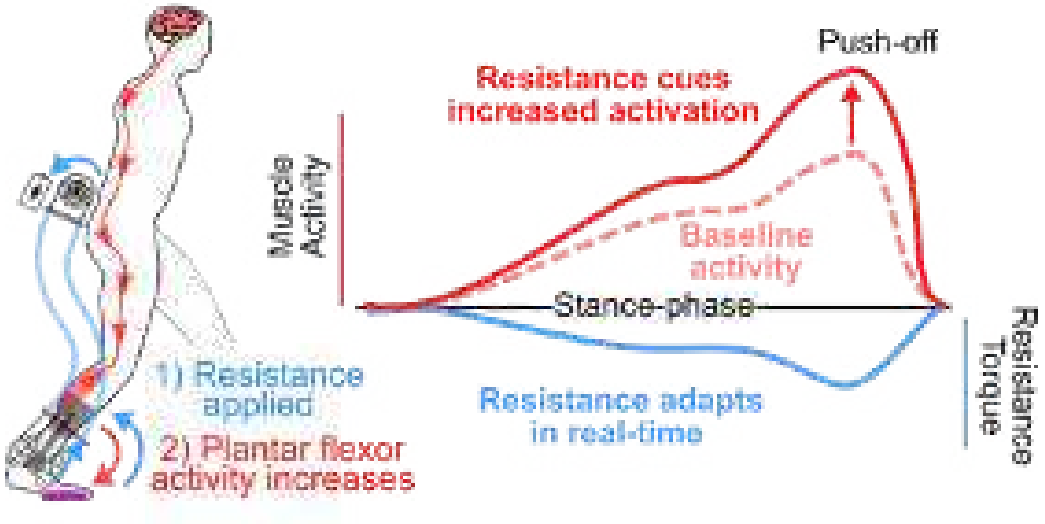
• Streamlined operation – automatic calibration allows users to turn on device and start walking



All-terrain assistance control – We have developed a proportional joint-moment control strategy capable of reducing the energy cost of over-ground walking [4] and operating seamlessly across the variable walking conditions encountered during daily life. This closed-loop approach utilizes embedded force sensors to provide intuitive, volitional control of exoskeleton assistance. As described above, this approach provides reliable, adaptive assistance by tracking demand placed on the biological joint. Two recent validation studies ([19] and In Review) demonstrates the ability of our control system to appropriately adjust RAAD assistance relative to the plantar-flexor muscle moment during accel/decel, level, incline, and decline walking at slow, medium, and fast speeds; stair ascent and descent; and 90° turning (**87.7 ± 2.7% average accuracy**, R = 0.96 ± 0.01 average correlation coefficient). This closed-loop control system offers a practical way to augment real-world walking performance without the need for complex classification.



Resist-to-Restore – We developed a purpose-built RAAD/SPARK resistance controller based on two primary design criteria. The first criterion was ***task-specificity***: the controller must facilitate increased neuromuscular firing of the plantar flexor muscles during the portion of the gait cycle when they function to propel the body forward (i.e. push-off). The second criterion was ***user engagement***: the controller should have minimal lag and provide a mechanical cue in response to changing user input (i.e. as someone pushes harder, more resistance is provided). To meet these goals, we implemented the inverse of our proportional joint-moment control scheme designed to provide adaptive resistance for a user to actively engage with during the stance phase of walking.



First to market – There are no commercially-available *wearable* powered assistive devices available for children. We seek to provide the first such device available to purchase for families, clinics, and hospitals. We also aim to provide a cost-effective and affordable device for sale prior to gaining reimbursement coverage, which we expect to take several years.

Intelligent design – The RAAD/SPARK device was designed to maximize improvements in mobility. This is accomplished through the use of lightweight materials, like carbon fiber, and mechanical design. Unlike uncomfortable wearable "exosuits" that rely on the garment's friction with the user's bare skin, the RAAD/SPARK device ankle assembly is self-supported and the reaction forces from the Bowden cables are transmitted to the ground. Furthermore, the heaviest components, including the motors and battery, are located near the waist, which minimizes the metabolic energy required to carry the additional mass [22]. The cables, and uprights of the RAAD/SPARK
have built-in adjustability in order to adapt as a child grows. Each RAAD/SPARK device will come with the necessary components to grow with a child for an entire year. Following growth spurts, lightweight components, like the cables, carbon fiber footplates, and calf cuffs can be easily exchanged.

RAAD User Interface: The RAAD's/SPARK's physical user interface includes an on-off switch and a toggle switch for "Assist-&-Go" or "Resist-to-Restore." The device needs to be initialized in
the phone app once per user by specifying their body mass, after which it can operate by the physical switch. The system automatically calibrates the foot sensors for the first three steps of walking, after which the torque gradually builds to the peak set point by 20% with each consecutive step. The app allows control of the torque setpoint; default assistive and resistive torque setpoints are 0.25 Nm/kg and 0.15 Nm/kg, respectively.

All-Terrain Control: Our intuitive RAAD/SPARK control scheme (Proportional Joint-Moment Control) is based on the principle of providing assistance as a function of the biological ankle moment [19]. High resolution force sensors placed under the ball of the foot and the automatic calibration procedure are used predict the biological ankle moment. We have validated this control strategy in individuals with and without CP during treadmill, over-ground, stepping, turning, incline, and decline walking (see preliminary data). We have demonstrated that this

control strategy can effectively reduce the metabolic cost of transport during over-ground walking [4]. No adverse
events have occurred.

The BiOMOTUM RAAD/SPARK device will be stored in the Center for Bionic Medicine department, room 1402 in a locked area that is only accessible to trained research staff.

It is determined that the study is not a significant risk with this device because of the safety measures that will be employed while using the device. While using the BiOMOTUM RAAD/SPARK device, research participants will be supported at all times with trained research staff and, when needed, a gait belt or a harness per the discretion of the research staff. This safety precaution is commonly utilized in physical therapy practice with other robotic training interventions as well as traditional approaches like walking on compliant surfaces or balance beam walking. Thus, it is felt that the utilization of the BiOMOTUM RAAD/SPARK, with the safety measures described, does not pose a significant potential for harming research participants.

PROCEDURES INVOLVED:

1. Screening/Baseline Procedures
    - 1.1 We will recruit up to 30 participants meeting the inclusion criteria. Recruitment will occur through Shirley Ryan AbilityLab's flagship hospital and all affiliate sites. We will also recruit form local physicians as well as the Cerebral Palsy Research Registry. Subjects will be divided into two groups: (a) always under therapist supervision and (b) with on therapist-supervised and two parent supervised sessions per week. Once subjects have agreed to participate in the study, they will be consented at the Shirley Ryan AbilityLab. Study staff will explain the study, a written consent form will be signed by the subject if 18 years or old (or by one parent/guardian if subject is under 18 years old). If subject is younger than 18 but older than 12, in addition to parental/guardian consent, the subject will provide verbal and written ascent to participate. Children younger than 12 will provide verbal ascent along with parental/guardian consent. A copy will be given to the subject while the original document will be kept in a secure, locked cabinet.
    - 1.2 Following informed consent, subjects will undergo physical evaluation and screening exam by trained research personnel. Study staff must obtain medical clearance from all subjects' physicians prior to baseline testing.
    - 1.3 Once they are enrolled, baseline outcome measures will be assessed by a trained research personnel.
2. Procedures during Treatment
    - 2.1 After the baseline testing is completed, subjects will begin 12 sessions of training, 3 sessions per week for 4 weeks (missing no more than 3 session's total). Up to an additional 3 training visits and/or 2-3 weeks may occur should the BiOMOTUM RAAD/BiOMOTUM SPARK/other similarly updated BiOMOTUM device require maintenance or updates during the child's participation. Additional visits should only be required if adjustment is needed to ensure safety following changes.

At minimum, 9 training visits can occur over 8 weeks. Training sessions will last up to 1 hour and will include walking training in the BiOMOTUM RAAD/SPARK device, with the device in resistance mode. Participants will be enrolled at GMFCS levels I-III, and randomly selected to complete the intervention in one of two modalities: (a) always under therapist supervision, and (b) with one therapist-supervised and two parent supervised sessions per week. All sessions, including those that are parent-supervised, will take place at Shirley Ryan AbilityLab. During parent-supervised sessions that seek to replicate how a child would train at home, parents will ask their child to walk with resistance to the best of their ability until the time is up. Parents can use toys and snacks to incentivize session completion.

Gait training will include approximately 20-30 minutes of treadmill walking; participants will complete three ~5-10-minute bouts of walking with seated rest periods in between. The research team will guide participants to walk at a moderate-to-high intensity for the duration of each walk as indicated by level 7 (“Hard”) on the Pictorial Children’s Effort Rating Table (PCERT). To maintain intensity as participants progress through the protocol, the therapist will increase the treadmill speed and/or the resistance level once per week to ensure progression. Plantar-pressure biofeedback will be provided to each participant at least once per session.

2.2 For both delivery modes, the therapist will increase the resistance level once per week to ensure progression.
2.3 During training and assessment sessions, the BiOMOTUM RAAD/SPARK iPhone will record data from the device’s joint angle and Inertial measurement Unit (IMU) sensors regarding the subjects ankle angles and body position.

Outcome Measures:

The following outcome measures will be collected by trained research personnel for all subjects at the following testing points: baseline, 2-7 days post-intervention (after 12 training sessions), and 3 weeks following the final training session.

Clinical Performance Outcome Measures:

1. **10 Meter Walk Test (10MWT):** The 10MWT assesses walking speed in meters per second over a short duration. Changes in gait speed that result in a transition to a higher category of ambulation classification resulted in better function and quality of life. In the 10MWT, subjects are directed to walk at their self-selected and maximum safe speed with effects of acceleration and deceleration minimized (by adding 1 meter at the beginning and at the end of the course to isolate the subject’s steady state speed). Any assistive device and orthotic should be kept consistent and documented. It should also be documented whether the gait is treated at “self-selected walking speed” or “fastest walking speed”. Three trials will be completed at the self-selected speed and three trials will be completed at the fast speed. If someone is unable to complete all trials, then the reason will be documented in the CRF.

2. 6 Minute Walk Test (6MWT): The 6MWT measures the distance a subject can walkindoors on a flat, hard surface in a period of 6 minutes, using assistive devices, as necessary. Any assistive device and orthotic should be kept consistent and documented. The test is a reliable and valid evaluation of functional exercise capacity and is used as a sub-maximal test of aerobic capacity and endurance. This test will be performed while walking without the device as well as with the BiOMOTUM RAAD/SPARK. It will be administered while wearing a mask to measure oxygen consumption (Cosmed K5B2 Metabolic Unit) when performed without the BiOMOTUM RAAD/SPARK. Electromyography may be used to assess lower-limb muscle activity during gait analysis trials and/or the 6MWT.

3. Timed Up and Go Test (TUG): The TUG assess mobility, balance, walking ability, and falls risk. The participant starts seated in a chair with his/her back against the chair back. On command, the participant rises form the chair, walks 3 meters, turns, walks back to the chair and sits down. Timing begins when the command to start is given and stops when the participant returns to a seated position. This test may be repeated up to 3 times during each assessment visit and during each training visit.

4. Gross Motor Function Measure -66 (GMFM-66): The GMFM-66 measures change in gross motor function over time in children with cerebral palsy. This assessment quantifies motor function, not the quality of the motor performance.

5. Gait Analysis: A quantitative means of assessing gait function based on spatiotemporal parameters of gait. The GAITRite system is an electronic walkway with integrated sensors and is considered a reliable and valid means of assessing gait changes post stroke. Electromyography will be used to assess lower-limb muscle activity during gait analysis. This includes adding small sensors to thighs, lower legs, and shins.

6. Muscle Strength Testing: The purpose of this test is to evaluate the strength of the legs by having the subject perform isometric, maximum contraction while the researcher provides a static, counterforce. A handheld dynamometer will be used to detect the minimum muscle strength change.

Self-Reported Measures:

1. **Patient Questionnaires:** This questionnaire will ask for the subject's feedback regarding their experience and satisfaction after using the BiOMOTUM RAAD/SPARK device.

   On the first follow-up visit, we will assess subjective user experience and quantify the usability of the device. Each research PT, participant and parent/guardian will complete the System Usability Scale (SUS). The SUS includes 10 statements rated by means of a 5-point Likert scale, from 1 (strongly disagree) to 5 (strongly agree), and the SUS scores have a range of 0 to 100 that is divided by five scales: score of 0–25: worst, score of 25–39:

poor, score of 39–52: OK, score of 52–85: excellent, and score of 85–100: best imaginable.

We will ask the participant to complete a custom, open-ended questionnaire with the following questions. Subjects have the right to refuse to answer to any questions they feel uncomfortable answering and the research team will mark these questions as unanswered.

(1) Did you see a benefit of training with the device?
   a. If yes, why?
   b. If not, why?
(2) How did training with the device make you feel?
(3) What were your favorite things about using the device?
(4) What were your least favorite things about using the device?
(5) Is there anything that would make the device better to use?

We will ask the parent/guardian to complete a custom, open-ended questionnaire with the following questions. Parents/guardians have the right to refuse to answer to any questions they feel uncomfortable answering and the research team will mark these questions as unanswered.

(1) Do you think your child enjoyed using the device?
   a. If so, what aspects were enjoyable?
(2) How did you perceive how training with the device made your child feel?
(3) Do you think there could be a benefit for your child to use such a device regularly during therapy?
   a. If so, how?

We will ask the lead research PT for each participant to complete a custom, open-ended questionnaire with the following questions:

(1) Do you think the device was effective in improving the gait training activities for this participant?
   a. If so, how?
   b. If not, why?
   c. Was there anything particular to this participant that influenced your response?
(2) Do you have any recommendations for how the device could have been more effective for this participant?

2. **Visual Analog Scale:** The 0-10 rating scale for pain is used to gain a subjective report of the intensity of a person's pain. Zero represents "no pain" and ten represents "the most intense pain imaginable". This will be in picture form using faces to depict the various levels of pain.

Wearable Sensors

1. **ActiGraph activity monitors:** These are devices with a small accelerometer that can be worn on a belt and/or on the ankle which can identify steps and kcals during daily activity. The Activity monitor's battery lasts 2 weeks. Each subject will be given an activity monitor for 2 weeks prior to initiation of training, wear the monitor during each therapy session, and for up to 3 months following intervention. Subjects will be given instructions on how to maintain the device, including charging instructions.

2. **Xsens:** Xsens Awinda system (Xsens Technologies BV, Enschede, Netherlands) is used for real-time inertial motion capture during walking and dynamic activities. Motion capture data is collected from 17 IMU modules mounted on subject's head, sternum, shoulders, upper and lower arms, hands, pelvis, upper and lower legs, and feet. Xsens's proprietary software MVN Analyze 2019 captures the IMU data at 60 Hz sampling frequency. From the recordings, the MVN Analyze suite allows to exact kinematic from 23 different body segments. The system has been validated for realtime, reliable and accurate human motion analysis
3. **EMG:** Muscle activity will be collected from subjects by electrodes placed upon the skin over specific muscles in the legs.

Video recording and/or pictures of each participant during assessments may be taken during the training and testing sessions. These items may be used to help troubleshoot potential issues. They may also be used for presentations and training of other research personnel. When feasible, attempts will be made to ensure the images or videos are devoid of any identifying information. Each subject may choose to limit if/how these items may be used, as indicated during their consent process.

DATA MANAGEMENT AND CONFIDENTIALITY

Data will be collected and kept confidential and compliant with HIPPAA requirements. All personal information and study documentation that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by a deidentified alphanumeric code. The "master list" linking personal information to the alphanumeric code will not be shared and will be kept separately in a secured location. All data will be captured in electronic format and stored on the secure and password protected network and devices managed by the Shirley Ryan Ability Lab. Electronic folders will be private with limited access as determined by the PI.

De-identified data will be stored indefinitely. If participants give written consent to be contacted for future studies, this information will be kept separate from de-identified data files, in locked cabinets accessible only by authorized research personnel. All other information will be destroyed in accordance with HIPAA and IRB compliant guidelines.

SHARING RESULTS WITH PARTICIPANTS

There is no intent to share information with participants. However, if a participant or guardian requests information about the individual results, the results of their outcome measures will be shared verbally. No results of other study participants will be shared to maintain patient confidentiality. Once results have been published, subjects may request those results in so far as that such is open to the general public.

STUDY TIMELINES

Study participation from initial consenting to post-intervention testing is anticipated to last up to 7 months, but may be longer based on subject availability. We anticipate ongoing enrollment over 3 years. Investigators will complete this study (primary analyses) 4 years from IRB approval

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

1. Diagnosis of cerebral palsy
2. GMFCS level I – III
3. Ability to walk for at least 6 minutes (assisted or unassisted)
4. Age between 8-21 years
5. Height/weight/BMI between the 5th - 95th percentile of children with CP
6. Able to understand and follow simple directions
7. Able to safely fit into a device configuration and tolerate assistance without knee hyperextension while walking
8. At least 20 degrees of passive ankle plantar flexion range of motion

Exclusion criteria:

1. Knee extension or ankle dorsiflexion contractures greater than 15 degrees
2. Health condition or diagnosis other than CP that would affect safe participation
3. Orthopedic surgery completed in the prior 12-months
4. Current enrollment in a conflicting research study

VULNERABLE POPULATIONS

No greater than minimal risk to children is presented. Parent or authorized guardian will be present during the consent process

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	Children	100	30
Study-wide	Children	100	30
Total:		100	30

RECRUITMENT METHODS

Participants will be recruited through a rolling referral beginning immediately after the approval of this protocol. Recruitment will end once the appropriate number of subjects has been enrolled. To account for a subject withdrawal from the study, 2-3 extra subjects will be recruited in order to ensure there are enough subjects to confirm the results. Shirley Ryan AbilityLab physicians and clinicians will refer their patients based on their clinical presentation.

Trained research staff who have access to medical records will mine the data and identify all persons with cerebral palsy treated at the Shirley Ryan AbilityLab who may be eligible to participate in this study. A research team member will approach, call, or email the potential participants/participant's legal guardian and introduce the study. If the patient/patient's legal guardian is interested in hearing more about the study, the team member will describe the project in detail. The team member will have recruitment flyers and a copy of the consent available for review. Per the potential participant's/participant's legal guardian's preference and continued availability, consenting procedures may occur at this time or a later time. If the patient/patient's legal guardian agrees to participate in the study, the team member will obtain written documentation of informed consent.

Shirley Ryan AbilityLab approved flyers will be hung at the facility to advertise the study. Clinicians at this location will be informed of the inclusion and exclusion criteria for this study in order to refer appropriate subjects. Information regarding this study will be posted on Shirley Ryan AbilityLab's available research studies webpage. Research Registries at Northwestern University and affiliates may also be utilized to find eligible participants. Potential research subjects will be referred to, and evaluated by, authorized research personnel. Potential research subjects will be identified based on inclusion and exclusion criteria. After identification of subjects based on inclusion and exclusion criteria, a verbal permission from the patient or authorized guardian will be obtained to request medical clearance from their physician.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Subjects will be seen for 12 training visits, with additional visits for screening, baseline and post-training evaluations, as well as up to 3 additional visits as needed. Each visit will last up to 4 hours. Subjects will be paid $50 per session for their study related visits and travel mileage to and from the Shirley Ryan AbilityLab. Compensation will be paid by Clincard from Shirley Ryan AbilityLab. Payments in excess of $600 in a calendar year are required to be reported as taxable income.

WITHDRAWAL OF PARTICIPANTS

Subjects will be withdrawn from the study in the event of a medical event or complication (i.e. hospitalization) that may alter the inclusion/exclusion criteria or which limits the patient from safely completing the remainder of the study, or at the discretion of the PI.

Subjects can voluntarily discontinue the study at any time. The participant will then be requested to notify the Principal Investigator, Dr. Arun Jayaraman, in writing or call at 312-238-6875, if assistance is needed in this process. Information collected prior to the study discontinuation by a participant may still be used by the research team.

The researchers reserve the right to discontinue study participation for any individual or for the study as a whole at their discretion.

RISKS TO PARTICIPANTS

All testing and training sessions will be under supervision of a trained researcher. Manual assistance or cueing will be provided as necessary for safety and balance. Vital signs will be monitored before and after physical exertion and during activities, as needed. All subjects will be permitted to stop physical activity or rest at any time during the study.

- The risk of falling: This could be caused by loss of control of ambulation by the participant or therapist as well as malfunction of the BiOMOTUM RAAD/SPARK device itself. The risk of falling will be minimized by having experienced SRALAB research personnel conduct the participant training sessions with manual assistance, and as needed overhead attachment with a safety harness and/or gait belt during over-ground gait training.
- Discomfort, skin pressure/friction, bruising, pain, or unusual swelling caused by the exoskeleton which has the potential to lead to skin breakdown or abrasions. This risk will be minimized by a thorough skin check performed by experienced research personnel at each training session. Adjustments to the device fit and additional padding will be assessed to decrease the risk of skin breakdown as well.
- There may also be a risk of skin irritation caused by the adhesives used to secure the sensors, EMG sensors, and IMUs to the participant. This will be reduced by careful monitoring of skin when these devices are utilized.
- Blood pressure instability during use of the device related to standing and walking activities during testing and training procedures. This risk will be reduced with frequent subjective assessment of patient's symptoms as well as assessment of blood pressure and heart rate prior to training, as necessary during training and following training. Activity will be stopped in the event of instability of vital signs and as recognized by experienced research personnel. Medical clearance will be required prior to any study related activities.
- Risk of exceeding range of motion: This would be caused if any device moves the Participant beyond the normal range of motion, resulting in a strain, sprain or fracture. For the BiOMOTUM RAAD/SPARK device, this risk is lessened by mechanical hard stops that prevent the device from exceeding a normal human range of motion even in the event of an electrical or software failure. Software systems are also in place to further reduce range of motion to improve fit and comfort during walking. Participants will be evaluated by clinicians who will eliminate Participants from being included in the study if Participants cannot meet the required range of motion. For all other devices, this risk will be mitigated through proper settings by the physical therapist in charge of Participants treatment.
- Spasms triggered by joint movement in the device. This risk will be reduced through screening prior to enrollment in the study. Participants cannot take part if the participant's muscles are too stiff.
- There is a risk of fractures when participating in a therapy program: this will be minimized by requiring medical clearance if participants are at risk for severe osteoporosis.
- The device itself could malfunction. All activities will be performed with close supervision from trained research personnel to monitor device function during use.
- The use of the BiOMOTUM RAAD/SPARK system may involve risks that are currently unforeseeable as this is a trial to assess use of the BiOMOTUM RAAD/SPARK device in the pediatric population with cerebral palsy.

POTENTIAL BENEFITS TO PARTICIPANTS There may be no direct benefit to the participants. The main benefit of this study is to better understand the use of technology to enhance gait ability of pediatric population with cerebral palsy.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Participants will be notified if any new information concerning the safety of the study device becomes available which may affect their decision to remain in the study. Participants will however be asked to perform all activities under the supervision of a trained research staff member.

DATA SAFETY AND MONITORING PLAN

The risks in this study are minimized by the use of extensive inclusion criteria and by close monitoring of the research subjects by experienced physical therapists. In addition, the primary research team is qualified and experienced in all of the study procedures. Nonetheless, since this study places the subjects at more than minimal risk, we utilize the services of a volunteer to serve as a Safety Officer at each sub-award research site.

1. **Safety Officer(s)**
    1. The Safety Officer at each research site will be solicited upon receipt of award and will be a faculty member from each sub-award location (NAU, Gillette, SRA Lab) who is experienced in clinical research. We will avoid conflict of interest by recruiting a person who is not affiliated with any member of the research team (i.e. not a collaborator)
    2. The Safety Officer will meet with study investigators twice annually. During these meetings, the following information will be reviewed:
        i. Adverse events report (see below)
        ii. Recruitment and enrollment statistics including the following information:
            1. Gender, ethnicity
            2. Number of subjects who were disqualified prior to randomization and reasons
            3. Number of subjects randomized
            4. Number of subjects who have withdrawn or been withdrawn from the study, and the reasons for withdrawal
            5. Number who subjects who have completed each phase of the study
    3. The Safety Officer will take minutes of the meeting, and after the meeting will distribute copies of the minutes to each of the investigators. The minutes will be reviewed at the beginning of the next Safety Officer meeting

2. **Adverse events reporting**

    The sub-award lead investigator (Dr. Lerner, Dr. Schwartz, and Dr. Jayaraman) will continually monitor all adverse events during the screening process and during procedures performed as part of this research.
    i. When a screening failure occurs, the individual will be contacted by the sub-award lead investigator and be informed of the reasons for screening failure.

ii. All adverse events will be reported to the safety officer monthly, and documented by standard IRB procedures and will be reported during the annual protocol review. Adverse events will be any event that does not satisfy the criteria for serious adverse events.

iii. All serious adverse events will be reported immediately to the safety officer, IRB Research Subjects Advocate, and the NIH, in a timely manner (e.g. within 48 h) using the IRB Serious Adverse Report Event (SAE) form. The PI will sign each SAE, and a copy of the consent form signed by the subject will be included, with relevant sections highlighted. Serious adverse events are defined as:
    1. Death
    2. Life threatening injuries
    3. Inpatient hospitalization
    4. Persistent or significant disability/incapacity
    5. Congenital anomaly/birth defect.

For all serious adverse events that are determined by IRB to be definitely, probably, or possibly related to the study or interventions, the IRB will take whatever action(s) it deems appropriate, including but not limited to:

1. Modification of the protocol
2. Modification of the consent form document
3. Modification to the timetable for continuing review requirements
4. Suspension of new enrollment into the study
5. Suspension or termination of the study - If the study is suspended or terminated, it will be promptly reported to the NIH institute that has provided funding for the study. All other events not requiring suspension or termination shall be reported during the annual progress report.

ClinicalTrials.gov Requirements
This study will be registered on ClinicalTrials.gov. All relevant findings will be reported at the end of the study.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Every possible precaution will be taken to protect the privacy interests of subjects. Participation in this study is completely voluntary. Trained research personnel will explain the purpose of the study and intended use of subject's personal health information and precautions taken to keep the study information and data confidential.

Subjects have the right to refuse to answer to any questions they feel uncomfortable answering and the research team will mark these questions as unanswered. Furthermore, participants can refuse other objective tests in the protocol however if the participants refuse the majority of tests which affect the overall implementation of the study, the participants may be withdrawn from the study at the discretion of the principal investigator.

COMPENSATION FOR RESEARCH-RELATED INJURY

If the participant has any injury or illness from the study device or the procedures required for this study, the reasonable medical expenses required to treat such injury or illness may be paid for by the study sponsor.

The coverage for such injury or illness is only available if the Northwestern University principal investigator and study sponsor have decided that the injury/illness is directly related to the study device or procedures and is not the results of a pre-existing condition or the normal progression of the participant's disease, or because they have not followed the directions of the study doctor. If the participant's insurance is billed, they may be required to pay deductibles and copayments that apply. The participant should check with their insurance company about any such payments.

ECONOMIC BURDEN TO PARTICIPANTS

Costs associated with participation in the study will be offset by payment for each in person session ($50 each training session and $50 for each assessment).

CONSENT PROCESS

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Should there be amendment made to the consent form after the initial signature of the original, the subject will be required to sign a new consent form at their next visit. A researcher will review the changes and discuss the implications of the change.

Prior to a patient's participation in the trial, the written informed consent form must be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The consent process will take place at the Shirley Ryan AbilityLab in Room 11-1402. Trained research personnel will guide the subject through consenting process. Subject will be given detailed explanation of the purpose, time line, commitment, procedures, data handling and privacy and confidentiality of information pertaining to the study.

NON-ENGLISH SPEAKING PARTICIPANTS

An interpreter who speaks the participant's primary language will be scheduled through the Shirley Ryan Ability Lab Interpreter Services department to attend all research appointments during which the participant is scheduled if necessary as determined by the participant.

PARTICIPANTS WHO ARE NOT YET ADULTS (infants, children, teenagers)

Participants will be asked their age upon study screen. Any child under the age of 18 years will be considered a minor. If the participant is determined a minor, every effort will be made to ensure the screening process proceeds with a parent or an authorized legal guardian present. The consent and protocol will be explained by a trained researcher to both the present parent/authorized legal guardian and the minor. The parent or authorized legal guardian will then be asked to consent on behalf of the minor, in accordance with the DHHS and the

USFDA's subpart D. The parent or authorized legal guardian will also be given the opportunity present at all training and testing sessions.

Consent will be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. This will be done to ensure the protocol is carried through in a timely manner.

Permission will also be obtained from an authorized legal guardian if necessary. Efforts will be made to determine whether the guardian is in fact legally authorized by ensuring the child lives with the aforementioned guardian.

Assent will be obtained from all children. Verbal assent will be obtained for children unable to give written consent. Assent will be documented in the IRB approved consent form.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

Subjects records will be kept completely confidential: Every possible precaution will be taken to protect the privacy interests of subjects. Participation in this study is completely voluntary. Trained research personnel will explain the purpose of the study and intended use of a subject's medical information and the precautions taken to keep the study information and data confidential. Data will be collected and kept confidential and compliant with HIPAA standards.

Participants will be assigned an alphabetical or numerical study ID. Identifying data will be kept in locked cabinets and password protected servers completely separate from de-identified data. Research data will be de-identified and stored in locked cabinets in the lab accessible only by authorized research personnel. Electronic data will be de-identified and kept on secure, password protected servers at the Shirley Ryan Ability Lab. Only authorized research staff will be able to access any of the formerly mentioned data. De-identified data will be kept indefinitely. Study documentation will be collected and stored and kept confidential and compliant with HIPAA requirements. Identifying data will be held for 7 years after the study is completed and published.

All personal information (names, addresses, email or phone numbers, etc.) gathered for this study that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The "master list" linking personal information to the alphanumeric code will not be shared, and will be kept by the study PI in a secure location. All personal information linking participants to their data will be destroyed after 7 years following the completion of the study.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The Shirley Ryan AbilityLab services the cerebral palsy population and is a research hospital that maintains a research registry (greater than 750 participants). In addition to our flagship hospital, we have outpatient clinics that provide long-term follow-up care to this population. We will recruit participants from our research registry, website and outpatient affiliates and facilities to meet our enrollment goal.

All study team members will be trained on the study protocol and procedures. Experienced physical therapists will lead the assessment and treatment sessions. The study team members are employees of the Shirley Ryan AbilityLab. They are familiar with the study site and are

experienced with the study population. There will be medical resources including a resident on call and nursing staff available 24 hours a day if needed in case of an emergency. All our treadmills have overhead harnesses for additional safety during training.

The principal investigator of this study, Arun Jayaraman, PT, PhD, is Director of the Max Nader Center for Rehabilitation Technologies and Outcomes (RT&O Lab), within CBM. Adequate dedicated office and treatment space is available for private meetings with potential subjects, performing physical evaluations, explaining the study protocol and obtaining study consent, performing data analysis, and writing manuscripts.

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ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☒ **Yes** ☐ No	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☐ Yes ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ No	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide*	
☒ **Yes** ☐ No **Approved by Gillette Scientific Review**	Require Scientific Review? Not sure? See guidance on next page.	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ Yes ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ Yes ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups**
☐ Yes ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	

☐ Yes ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu* *Contact:*	**each have their own application process.**
☐ Yes ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ No **Approved by Gillette Compliance Review**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ Yes ☒ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ Yes ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: cdrifka@umn.edu*	
☐ Yes ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ No **Registration on clinicaltrials.gov will be managed by the prime site/sponsor (BiOMOTUM, Inc.)**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	

☐ **Yes** ☒ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff Contact: oncore@umn.edu*	**Does not affect IRB approval.**

Protocol Title	Development of a robotic ankle assist device to improve mobility in individuals with movement disorders
Principal Investigator/Faculty Advisor	Name: Michael H. Schwartz
	Department: Gillette Children's Specialty Healthcare, Center for Gait and Motion Analysis; University of Minnesota, Department of Orthopedic Surgery
	Telephone Number: 651-229-3929
	Email Address: mschwartz@gillettechildrens.com; schwa021@umn.edu
Student Investigator	Name: N/A
	Current Academic Status (Student, Fellow, Resident):
	Department:
	Telephone Number:
	Institutional Email Address:
Scientific Assessment	Nationally-based, federal funding organizations Approved by Gillette Scientific Review
IND/IDE # (if applicable)	N/A
IND/IDE Holder	N/A
Investigational Drug Services # (if applicable)	N/A
Version Number/Date:	V11, 11/09/2022

PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
10/11/2021	v2	Addition of recruitment flyer	No
11/29/2021	v3	Update language for experiments 1 and 2; inclusion and exclusion criteria updated	Yes
02/01/2022	V4	Update language for exploratory phase and experiments 1 and 2, addition of questionnaires to experiment 1 and 2; inclusion and exclusion criteria update; addition of UBACC to assess capacity to consent	Yes
03/02/2022	v5	Addition of documentation of study participation (consent) in medical record; Update inclusion criteria	Yes
06/15/2022	V6	Addition of mileage reimbursement	Yes
7/6/2022	V7	Increase participant remuneration and addition of hotel reimbursement;	Yes
7/14/2022	V8	Language for hotel reimbursement has been updated to reflect funding source policy	Yes
7/29/2022	V9	Physical therapist added as part of initial contact to participant	No
9/13/2022	V10	Update frequency and Surgery Requirement	Yes
11/09/2022	V11	Update screening language	Yes

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ABBREVIATIONS/DEFINITIONS

- ABS — Ankle brace system
- CP — Cerebral Palsy
- EMG — Electromyography
- GMFCS — Gross Motor Function Classification System
- LAR — Legally authorized representative
- MRN — Medical Record Number
- PT — Physical therapy; Physical therapist
- ROM — Range Of Motion

1.0 Objectives

1.1 Purpose:

The purpose of this investigation is to establish the feasibility and efficacy of a lightweight, battery-powered ankle brace system (ABS) to improve mobility for individuals with cerebral palsy (CP).

- Aim 1: Complete a personal-use feasibility analysis of the ABS. This aim will be completed by collaborators at Northern Arizona University and BiOMOTUM, Inc. (prime site/sponsor), and activities will be covered by a separate IRB protocol.
- Aim 2: Gather feedback from Aim 1 to design and prototype a minimum viable ABS for use in clinical and community settings. This aim will be completed by collaborators at Northern Arizona University, Shirley Ryan Ability Lab, and BiOMOTUM, Inc., and activities will be covered by separate IRB protocols.
- Aim 3: Quantify the potential for an ABS to increase the effectiveness of clinical gait therapy by targeted *assistance* and *resistance* training. **This aim will be completed by Gillette Children's Specialty Healthcare (Gillette), and activities will be covered by this IRB protocol.**

2.0 Background

2.1 Significance of Research Question/Purpose:

Many of the 500,000 children in the United States with CP, the most common cause of pediatric physical disability, have difficulty walking and participating in physical activity. Half of all ambulatory children with CP lose the ability to walk independently in adulthood, indicating that the current approaches for treating these individuals do not result in meaningfully improved mobility over time. Physical therapy (PT) is essential for treating CP, but the amount of PT is generally insufficient, and the delivery of PT can be inefficient. There is currently no viable way to provide a sufficient dose of PT that will lead to long-term improvements in mobility and reduce the negative physical and social outcomes related to limited mobility and reduced physical activity.

Due to the lack of available and sufficient treatment methods for improving mobility, the study team aims to establish the feasibility and efficacy of an ABS for *assistance* and *resistance* training. In the long-term, this research will improve our ability to optimize the prescription of wearable assistive devices to improve mobility and increase physical activity in individuals with movement disorders.

2.2 Preliminary Data:

Past work completed by our collaborators has shown improvements in walking outcomes following treadmill and over-ground *assistance* interventions using a powered ABS. In a pilot study conducted using an instrumented treadmill, five participants with CP (5-30 years old) practiced walking at self-selected speeds with powered plantarflexor assistance. Participants exhibited a 19% reduction (p<0.05) in net metabolic cost of transport on average during treadmill walking with assistance compared to their baseline walking condition. Compared to baseline, participants also had reduced crouch by 14.4 ± 4 degrees (p<0.05) across the lower extremities, increased positive ankle power by 43.6 ± 7.4% (p<0.05), and decreased positive hip power by 29.2 ± 6.0% (p<0.01).[1] All these changes are biomechanically favorable.

Further, in a pilot study to test the powered ankle brace *resistance* therapy, participants completed 10 training sessions over 4 weeks with progressively increasing levels of resistance. Participants exhibited significantly improved (reduced) stance-phase ankle co-contraction by 29% ± 13% (p<0.04) and a more normal plantarflexor muscle activation profile by 30% ± 15% (p<0.02). Additionally, an increase in neural control complexity of walking after training was observed, which was significantly greater than a matched control group that underwent standard orthopedic and neurologic surgery alone. These improvements in neuromuscular control are indicative of a more mechanically efficient gait pattern, improved metabolic cost, and enhanced functional performance.[2,3]

2.3 Existing Literature:

Children with CP frequently experience a downward trend of reduced physical activity and worsening gait, leading to a permanent decrease or loss in ambulatory ability.[4] For children with CP, walking is drastically more energetically expensive than for their typically developing peers.[5] Experts have called for new ways to elevate activity levels in children with movement disorders.[6,7]

The ankle joint plays a critical role during walking, acting to stabilize, support, and propel the body.[8] Activation of the ankle plantarflexor muscles is reduced, less modulated, and often accompanied by co-activation of the antagonist dorsiflexor muscles in most individuals with spastic CP. Reduced ankle performance during walking in children with CP is suggested as a primary contributor to the observed gait dysfunction.[9] Ankle plantarflexors of children with CP produce 50% less positive joint work than in typical gait,[10] resulting in a reliance on more proximally located muscles for forward progression.[11] These muscle activation characteristics likely contribute directly or indirectly to reduced energy exchange,[12] elevated metabolic cost of transport,[13] and lower levels of physical activity[14] in this patient population. Evidence suggests that addressing or augmenting the neuromuscular

deficits at the ankle may allow children with CP to engage in greater amounts of habitual physical, which would likely have many additional physical and mental health benefits.[15,16]

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

Activities collected at Gillette and will be split into an Exploration phase and an Experimental phase (split into Experiments 1 and 2), each with different outcomes:

- Exploration: Qualitative participant assessment of device usability, device comfort, and ease of donning/doffing.
- Experiment 1: Number of steps with mean late stance (i.e., propulsive) ankle plantarflexor activity above pre-session baseline average activity of 5 heel raises
- Experiment 2: Preferred walking speed and similarity of muscle activity to the average unimpacted activity pattern calculated via cross-correlation coefficient

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

- Exploration: N/A
- Experiment 1: Number of steps with mean stance phase ankle co-contraction below pre-session baseline
- Experiment 2: Metabolic cost; six-minute walk test (6MWT); timed up-and-go test (TUG); gait kinematics and kinetics; stride-to-stride variability of lower-extremity muscle activity; variance accounted for by the first muscle synergy; plantarflexor muscle strength; 66-item Gross Motor Function Measure (GMFM-66)

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

Both the Exploration and Experimental phases will test the use of the ABS within the context of device usability and ease (Exploration), therapy precision (Experiment 1), and *assistance* training (Experiment 2). Participants may partake in any study phase in which they are eligible, and participation in each experiment may take place in any order.

Exploration:

In the Exploration phase, participants will come to Gillette for up to two visits. These visits will include ABS fitting and acclimation to test device usability, device comfort, assisted vs. unassisted walking performance, and ease of

donning/doffing. This exploratory work will allow participants to test the ABS, and a licensed physical therapist (PT) will be present. To explore a participant's accommodation to the device, the PT, at their discretion, may use electromyography, metabolic measurements, and/or 10 m and 6 minute-walk-tests. Participant, parent/guardian, and therapist questionnaires may be provided. If interested and eligible, they would be invited to participate in Experiments 1 and 2, although participation in the Exploration phase is not a requisite for participation in Experiments 1 and/or 2.

Experiment 1:

In Experiment 1, participants will come to Gillette for a baseline visit. This baseline visit will include ABS fitting and acclimation. Following the baseline visit, participants will return to Gillette for 3 additional visits in a randomized order: assistance visit, resistance visit, and typical gait therapy visit. During each visit, a licensed PT will guide participants through the following activities while collecting plantarflexor activity via surface electromyograph (EMG): 10 minutes of treadmill walking, 10 minutes of overground walking, and 15 minutes of walking skills practice (e.g., sideways, backward, stepping strategies, etc.).

Experiment 2:

In Experiment 2, participants will come to Gillette for a baseline visit. Like Experiment 1, this baseline visit will consist of ABS fitting and acclimation. Following the baseline visit, participants will return to Gillette for 12 visits with *assistance* training. Assistance training will include approximately 20-30 minutes of overground walking with assistance monitored by the PT; participants will complete three ~5-10-minute bouts of walking with seated rest periods in between. The research team will guide participants to walk at a moderate-to-high intensity for the duration of each walk as indicated by level 7 ("Hard") on the Pictorial Children's Effort Rating Table (PCERT).[18]

After all assistance training visits are complete, participants will complete follow-up visits at 3 days and 3 weeks post-training. At the baseline and follow-up visits, the participants will complete the following activities guided by a PT: standard three-dimensional gait analysis (e.g., metabolic cost, 6MWT, gait kinematics and kinetics, surface EMG, and physical examination), TUG, and GMFM-66 dimensions D and E (e.g., walking, running, and jumping activities).

Participants must complete at least 1 visit per week and miss no more than 3 visits total.

4.2 Drug/Device Handling:

The ABS is a lightweight battery-powered ankle orthosis. The system includes a torque sensor, system controller, battery, cables, calf cuff and frame, foot plate, and sensor inserted in a shoe (Figure 1A). The complete ABS system has a total mass of 1.5 kg (70% of mass situated in a waist pack or backpack) and allows the user to move around freely (Figure 1B).

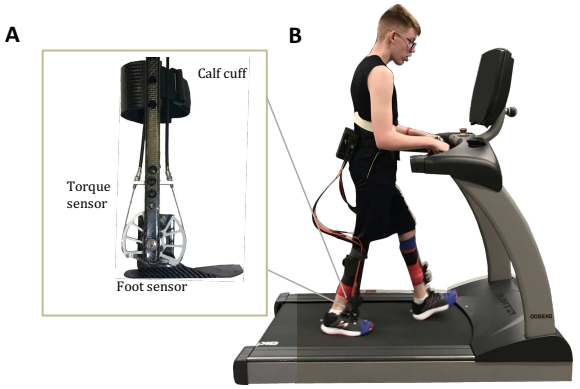

Fig 1. Ankle Brace System (ABS). **A.** ABS with a torque sensor, calf cuff and frame, and foot plate and sensor to be inserted in a shoe. This is similar in size to a standard AFO. **B.** Complete ABS with waist battery pack, cables, and components in A. Participant is wearing the complete system while walking on a treadmill. Figure provided by collaborators at NAU.

The ABS provides a small amount of motorized assistance that is intended to augment existing activity. This and other similar investigational devices have been classified by the Food and Drug Administration as a *nonsignificant risk device* because they do not meet the definition of significant risk under 812.3(m) of the investigational device exemption (IDE) regulation (21 CFR 812 and outlined in HRP-418 Checklist: Non-Significant Risk Device). In other words, the ABS:

- is not an implant;
- is not supporting or sustaining life;
- is not used for diagnosing/curing/mitigating/treating disease; and
- does not present the potential for serious risk to health or safety.

Additionally, several safety precautions are implemented to ensure participant safety, including mechanical “stops” to prevent hyperextension of joints, an emergency stop button that shuts off power to the device, and embedded software mechanisms that shut off power to the device if the user were to fall.

Following 21 CFR 812.2 (as outlined in HRP-307 Worksheet: Medical Devices), the ABS fits within the *abbreviated IDE requirements* as:

- our activities are testing the safety and efficacy of the ABS;
- it is a nonsignificant risk device;
- it is not banned from use by the FDA; and
- informed consent and documentation of informed consent will be obtained from all participants. A comment of study participation will be made in the participants medical record as communication with other hospital staff.

Further, following the requirements for an abbreviated IDE, the investigator will follow regulations and reporting requirements as appropriate (21 CFR 812.150). At the end of the study, the investigator will be responsible for returning products to the prime site/sponsor and submitting a final report to the appropriate IRB.

4.3 Biosafety:

N/A

4.4 Stem Cells:

N/A

4.5 Fetal Tissue:

N/A

5.0 Procedures Involved

5.1 Study Design:

Prospective cohort study

5.2 Study Procedures:

Potential participants will be identified and screened by study team members by reviewing the Gillette medical record as well as the Gillette Center for Gait and Motion Analysis database and schedule. Potential participants may be contacted by introductory letter, phone call, or in-person during a standard of care clinic visit to determine interest in any phase of the study. If a potential participant is interested, study team members will follow-up to answer questions, determine eligibility, and schedule research visits as appropriate.

All activities proposed in this protocol are for research purposes only. Potential participants will come to the Gillette for their research visits. Informed consent

and assent will be obtained prior to any study activities as outlined below. Breaks will be provided to participants as needed.

Exploration:

For the Exploration phase, participants will come to Gillette for up to two visits. These visits will include ABS fitting and acclimation, which may take up to 60 minutes each visit. Participants will walk with the unpowered and powered ABS to assess device usability, device comfort, and ease of donning/doffing. Additionally, they will complete a qualitative assessment to document their experience. This exploratory work will allow participants to test the ABS and provide feedback to investigators prior to the Experimental phase. A licensed PT will be present to assist as needed. If interested and eligible, participants of the Exploration phase would be invited to participate in Experiments 1 and 2, although this participation is not a requisite for Experiment 1 and/or 2 participation.

Experiment 1:

For Experiment 1, participants will come to Gillette for a baseline visit. This baseline visit will include ABS fitting and acclimation, which will take roughly 60 minutes. No full gait analysis is needed because comparison is primarily between the three sessions for relative changes in surface EMG. Participants will walk with the unpowered ABS to assess comfort and fitting. The device will be adjusted to fit each participant. A short unassisted/unresisted walking bout will be completed and the device further adjusted for comfort. Once fitted properly, each participant will walk for 10 minutes with *resistance* and 10 minutes with *assistance*. The magnitude of resistance and assistance will be gradually increased until the participant's preferred levels are established. These levels will be recorded and used for the following visits. Breaks will be provided, as needed.

Following the baseline visit, participants will return to Gillette for 3 additional visits over 3 weeks: assistance visit, resistance visit, and typical gait therapy visit. The order of these 3 visits, which will take roughly 90 minutes each, will be randomized. The visits will be conducted by a licensed PT. During each visit surface EMG electrodes will be placed, and instrumented insoles will be used in the participant's shoes to record step count. Participants will complete a baseline walking trial on a treadmill at the same self-selected speed established on the first visit. The PT will guide participants through the following activities and collect the outcome measures listed in sections 3.1 and 3.2:

- 10 minutes of treadmill walking with a focus on plantarflexor engagement and lower-extremity posture

- 10 minutes of overground waking with a focus on stride length and inter-limb symmetry
- 15 minutes of walking skills practice (e.g., sideways, backward, stepping strategies, etc.)

The study team will make every effort to have the same PT conduct all visits for each participant to minimize variability between sessions. The participant and PT will complete a questionnaire at the end of each session.

Experiment 2:

In Experiment 2, participants will come to Gillette for a baseline visit which will take roughly 120 minutes. Baseline visit will include a complete gait analysis and ABS fitting and acclimation. Additionally, this baseline visit will be used to collect outcome measures as described below.

Following the baseline visit, participants will return to Gillette for 8-12 training visits over 4-8 weeks with *assistance* training, which will take roughly 30-60 minutes each. During each of the training visits, participant will don the RAAD the PT will guide participants through the following activities (breaks will be provided, as needed):

- Three bouts of ~5-10 minutes of overground walking with assistance at moderate-to-high intensity.

After all assistance training visits are complete, participants will complete a follow-up visit at 3 days and 3 weeks post-training visits.

During the baseline and follow-up visits, the PT will guide participants through the following activities and collect the outcome measures listed in sections 3.1 and 3.2:

- Three-dimensional gait analysis, which includes steady-state metabolic cost on a treadmill (if tolerated), 6MWT, gait kinematics and kinetics, markers and surface EMG, and physical examination and medical history – Clinically validated method for collecting and analyzing gait and motion in the Gillette Center for Gait and Motion Analysis
- TUG, which measures the time required to stand up for a standard arm chair, walk 3 meters, turn, walk back to the chair and sit down – Clinic measure of balance and functional mobility
- GMFM-66, which measures gross motor activities across five dimensions such as lying/rolling, sitting, crawling/kneeling, standing, and

walking/running/jumping – Clinically validated assessment of changes in gross motor function of children with CP (CanChild)

The study team will make every effort to have the same PT conduct all visits for each participant to minimize variability between sessions.

On the first follow-up visit, we will assess subjective user experience and quantify the usability of the device. Each research PT, participant and parent/guardian will complete the System Usability Scale (SUS).[19] The SUS includes 10 statements rated by means of a 5-point Likert scale, from 1 (strongly disagree) to 5 (strongly agree), and the SUS scores have a range of 0 to 100 that is divided by five scales: score of 0–25: worst, score of 25–39: poor, score of 39–52: OK, score of 52–85: excellent, and score of 85–100: best imaginable.[20]

We will ask the participant to complete a custom, open-ended questionnaire with the following questions. Subjects have the right to refuse to answer to any questions they feel uncomfortable answering and the research team will mark these questions as unanswered.

(1) Did you see a benefit of training with the device?
    a. If yes, why?
    b. If not, why?
(2) How did training with the device make you feel?
(3) What were your favorite things about using the device?
(4) What were your least favorite things about using the device?
(5) Is there anything that would make the device better to use?

We will ask the parent/guardian to complete a custom, open-ended questionnaire with the following questions. Parents/guardians have the right to refuse to answer to any questions they feel uncomfortable answering and the research team will mark these questions as unanswered.

(1) Do you think your child enjoyed using the device?
    a. If so, what aspects were enjoyable?
(2) How did you perceive training with the device made your child feel?
(3) Do you think there could be a benefit for your child to use such a device regularly during therapy?
    a. If so, how?

We will ask the lead research PT for each participant to complete a custom, open-ended questionnaire with the following questions:

(1) Do you think the device was effective in improving the gait training activities for this participant?
   a. If so, how?
   b. If not, why?
   c. Was there anything particular to this participant that influenced your response?

(2) Do you have any recommendations for how the device could have been more effective for this participant?

5.3 Study Duration:

Activities at Gillette will occur in years 2 and 3 of the overall award. Gillette is participating in Aim 3 of the overall award; previously described in section 1.1.

Screening and recruitment at Gillette will take 6-12 months and data collection will take an additional 10-12 months.

Data analysis and dissemination will occur in the last 6 months of the overall award.

5.4 Use of radiation:

N/A

5.5 Use of Center for Magnetic Resonance Research:

N/A

6.0 Data and Specimen Banking

6.1 Storage and Access:

Data will be stored electronically using secure methods and as hard copy forms in locked offices/file cabinets. Data collected as part of the three-dimensional gait analysis will be collected, stored, and processed in the Gillette Center for Gait and Motion Analysis database as standard practice. Other remaining data, such as demographic, ABS, or other research records will be stored in electronic and hard copy research records.

Electronic data collected at Gillette will be stored and on secure Gillette shared internal networks, REDCap, and UMN Box. To minimize errors and ensure accurate data analysis, identifiable data will be shared with collaborators. This data sharing will be done using HIPAA-compliance methods like email and UMN Box throughout the study duration.

After the study is complete, we will destroy direct identifiers and linking information but will retain and preserve de-identified data. Individual and

aggregate data may be shared publicly if required by federal regulation, funding agency, or publishing entities.

6.2 Data:

- Demographic and medical history - Data will be collected, stored, and processed electronically in research records and the Gillette Center for Gait and Motion Analysis database as standard practice. Data include, but is not limited to, demographic information, date of birth, height, weight, medical and surgical history, and diagnoses.
- Three-dimensional gait analysis - Data will be collected, stored, and processed electronically in the Gillette Center for Gait and Motion Analysis database as standard practice. Data include TUG, gait kinematics and kinetics, 6MWT, surface EMG, and physical examination measures.
- ABS - Data will be collected, stored, and processed electronically in research records. Data include, but is not limited to, level of assistance and resistance, and step count.
- Other research records (e.g., enrollment logs, etc.) - Data will be collected, stored, and processed electronically in research records or saved as hard copy forms. Hard copy forms will be transcribed electronically as appropriate and will be stored in locked offices/file cabinets.

6.3 Release/Sharing:

Study-wide, team members are affiliated with either Gillette, Northern Arizona University, Shirley Ryan Ability Lab, or BiOMOTUM, Inc. Data collection related to Gillette participants will only occur at Gillette. Further, Gillette study team members have access to medical records as a function of their job duties.

Identifiable data will be shared with collaborators (e.g., name, date of birth, date of service, diagnosis, etc.) using secure and HIPAA-compliant methods throughout the study duration, including encrypted email and UMN Box.

After the study is complete, de-identified individual and aggregate data may be shared publicly in ways that will not identify the individual. This will follow federal regulation, funding agency requirements, and publishing requirements.

7.0 Sharing of Results with Participants

7.1 Sharing of Results:

Individual results will not be shared with participants.

Periodic study updates may be mailed to participants. No individual responses will be shared in these summaries and all study updates will be IRB-approved prior to mailing.

8.0 Study Population

8.1 Inclusion Criteria:

Exploration:

- 8-21 years old
- Height/weight/BMI between the 5th – 95th percentile of children in the Gillette Center for Gait and Motion Analysis database
- Able to walk for at least 6 minutes (assisted or unassisted)
- Able to understand and follow simple directions
- Able to safely fit into device configuration and tolerate assistance without knee hyperextension while walking

Experiments 1 and 2:

- Diagnosed with cerebral palsy
- 8-21 years old
- GMFCS I-III
- Height/weight/BMI between the 5th – 95th percentile of children with CP in the Gillette Center for Gait and Motion Analysis database
- At least 20 degrees of passive ankle planter flexion range of motion
- Able to complete at least 1 heel raise with minimal assistance (balance only)
- Able to walk for at least 6 minutes (assisted or unassisted)
- Able to understand and follow simple directions
- Able to safely fit into device configuration and tolerate assistance without knee hyperextension while walking
- Minimal invasive orthopedic surgery

For Experiments 1 and 2, we will recruit an equal number of males and females, matched by age within 2 years.

8.2 Exclusion Criteria:

Exploration:

- Consenting individual and participant non-English speaking and reading
- Total knee or ankle ROM less than 15 degrees at each joint
- Health condition or diagnosis other than CP that would affect safe participation
- Orthopedic surgery completed in the past 12 months
- Current enrollment in a conflicting research study

Experiments 1 and 2:

- Consenting individual and participant non-English speaking and reading
- Total knee or ankle ROM less than 15 degrees at each joint

- Health condition or diagnosis other than CP that would affect safe participation
- Major orthopedic surgery completed in the past 12 months
- Current enrollment in a conflicting research study

8.3 Screening:

A list of potential participants will be generated from Gillette medical record and Gillette Center for Gait and Motion Analysis database and schedule. Potential participants may also be referred to study staff by hospital providers or through recruitment flyers and social media. Data stored in the Gait and Motion Analysis database will be used to determine eligibility. Potential participants will be screened for eligibility by delegated and trained study team members. Potential participants that are determined eligible will be contacted by introductory letter, phone call, and/or in-person during a standard of care clinic visit to determine interest. If a potential participant is interested, study team members will follow-up to answer questions, determine eligibility, and schedule research visits as appropriate. If a potential participant does not have previous data in the Gait and Motion Analysis database, they will be asked to come in for a screening visit to determine if the device fits and determine eligibility. Individuals who come in for a screening visit will be asked to complete a consent form regardless of whether they are enrolled into the study or not.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	**Targeted Population**
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric	Excluded from Participation

disorders, neurologic disorders, developmental disorders, and behavioral disorders	
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Excluded from Participation
Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation
Undervalued or disenfranchised social group	**Included/Allowed to Participate**
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded from Participation
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	**Included/Allowed to Participate**
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded from Participation
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	**Included/Allowed to Participate**
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might	Excluded from Participation

influence consent to research or decision to continue in research.	

9.2 Additional Safeguards:

Cerebral palsy is a common neuromuscular disorder that develops during childhood and persists throughout the lifetime. Diagnosis, medical decision-making, and treatment often occur during childhood and adolescence, making children the population of interest.

This study involves no greater than minimal risk, so only one legally authorized representative (LAR) will provide consent for the minor participant. It will be communicated to participants and their LAR that participation in the research study is voluntary during the informed consent process. The child participant or LAR can indicate if they wish to discontinue participation at any point.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

In total, up to 50 participants may be consented into the study conducted at Gillette, which includes the Exploration phase and Experimental phase.

Up to 20 participants may be consented into the Exploration phase. This is a sample of convenience and is preparatory to Experiments 1 and 2.

Up to 15 participants may be consented into each Experiment (i.e., up to 30 total) to account for possible attrition and incomplete data. This will ensure we reach our recruitment goal of 12 enrolled participants with complete data in each Experiment.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

Gillette study team members may contact potential participants via an introductory letter and recruitment flyer, phone call, and/or in-person during a standard of care visit to explain study and determine interest. If a potential participant is interested, study team members will follow-up to answer questions, determine eligibility, and schedule research visits as appropriate. Email communication will be utilized when possible.

11.2 Identification of Potential Participants:

Potential participants will be identified through a screening of the Gillette medical record and the Gillette Center for Gait and Motion Analysis database and schedule. Gillette study team members have access to the medical record as a

function of their job duties, and trained research team members are permitted to review PHI for activities preparatory to research. No PHI will be removed from Gillette and only the information necessary to determine study eligibility will be used.

The study coordinator and/or study physical therapist at Gillette will be the primary study team members contacting potential participants to introduce the study. However, any study team member at Gillette indicated as being involved in consent may contact participants as well.

Of note, collaborators will not be involved with participant contact or activities.

11.3 Recruitment Materials:

A study team member, most often the study coordinator and/or physical therapist, will make initial contact with potential participants by sending an introductory letter and recruitment flyer, discussing in-person during a standard of care visit, and/or calling on the phone.

11.4 Payment:

For participants in the Exploration phase, they will not receive compensation. For participants in Experiment 1, they will receive $50 compensation per visit for 4 visits ($200 per participant). For participants in Experiment 2, they will receive $40 compensation per visit for 15 visits ($600 per participant). These dollar amounts are similar to past Gillette studies with similar time and effort commitments. Additionally, participants will be reimbursed for roundtrip mileage at the current federal rate. Hotel and parking will be offered to families that travel overnight and are traveling from a distance of 100 miles or more from Gillette. Hotel and parking costs will be covered up to the current federal rate. A Gillette travel agent will help book each participants hotel stay.

Payment will be made via the Greenphire ClinCard, and appropriate language describing the Greenphire ClinCard has been added to the consent forms as appropriate.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants will be withdrawn if they are later identified as not meeting the inclusion criteria (e.g., identified as eligible in error), if they miss more than 3 research visits in a given Experiment, or if they decide to stop participating in the study.

12.2 Withdrawal Procedures:

If a participant consents to the study but elects to stop participating after data collection has started, any data that was collected will be retained unless the participant asks otherwise.

Participants must alert the study team in writing of their request to be withdrawn from the study.

12.3 Termination Procedures:

Data collected and completed up to the point of withdrawal or termination will still be included in the study unless the participant asks otherwise.

13.0 Risks to Participants

13.1 Foreseeable Risks:

The potential minimal risks associated with this study are as follows:

First, is the risk of falling during ambulatory activities performed during this protocol but this is no greater than during normal daily life. Additionally, this risk will be minimized by supervision from a licensed PT and the use of a safety harness and/or walker for unstable participants.

Second, is the risk of fatigue, shortness of breath, or muscle soreness during or after the research visits. It is expected that when these symptoms occur, they will be minor and brief. If a participant experiences excessive shortness of breath or fatigue, they will be allowed to stop and given adequate rest before continuing. Should the participant experience any muscle soreness, light stretching, and hot/cold therapy will be recommended to reduce soreness. If these approaches do not alleviate the soreness, we will advise the use of OTC pain relievers (e.g., aspirin, acetaminophen, ibuprofen), unless contraindicated. As previously mentioned, a licensed PT will be present at each research visit.

Third, there is a risk of stumbling or falling while walking with the ABS. The amount of ankle assistance/resistance is not designed or able to completely over-power the user. As previously mentioned, several safety precautions are implemented to ensure participant safety, including mechanical “stops” to prevent hyperextension of joints, an emergency stop button that shuts off power to the device, and embedded software mechanisms that shut off power if the user were to fall. Lastly, a licensed PT will be present at each research visit.

Fourth, there is a small risk of loss of confidentiality as part of participating in research. Study team members are trained on appropriate data use and storage, and every reasonable effort is made to minimize risk associated with loss of privacy and confidentiality.

13.2 Reproduction Risks:

N/A

13.3 Risks to Others:

N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

Potential benefits for this study include determining if wearable ankle assistance or resistance are viable treatment strategies for our participants, which can be used to guide future treatments and therapy and possible improvement in mobility.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

Data will be collected and analyzed by Gillette study team members and collaborators.

Exploration:

As described below, the Exploration phase is a sample of convenience, and these activities are preparatory to the Experimental phase.

Experiments 1 and 2:

For Experiments 1 and 2, power analyses were used to determined estimated sample sizes. Statistical procedures include Repeated Measures ANOVA (RM-ANOVA) and generalized linear models. Participants in each Experiment will be age-, GMFCS-, and sex-matched as appropriate to control for known and unknown covariates. Participant demographics and baseline characteristics will also be analyzed.

15.2 Power Analysis:

Exploration:

No power analysis was done for the Exploration phase; this is a sample of convenience.

Experiment 1:

The sample size for the primary outcome measure in Experiment 1, mean stance phase plantar-flexor activity, was determined for the Repeated Measures ANOVA (RM-ANOVA). We set the Type II error rate (beta) at 0.2, and therefore the power level at 0.8 and alpha at 0.05. Sample size was determined based on the difference in soleus activity (45 ± 35%) from our collaborators preliminary ABS resistance validation study. We found that a subject sample size of n = 10 will

allow us to find significance. We will enroll and collect complete data for 12 participants to provide an adequate sample for our investigation into participant characteristics that will be correlated with outcomes.

Experiment 2:

The sample size for the primary outcome measures in Experiment 2 was determined for the RM-ANOVA using our preliminary over-ground RAAD assistance training study (speed: 24±10%; normality of soleus profile: 39±20%; see section 2.2 Preliminary Data). We found that a sample size of n = 5 will allow us to find statistical significance for the assistance training protocol. We will enroll 12 participants to provide an adequate sample for our investigation into participant characteristics (i.e., covariates) that will be correlated with outcomes.

15.3 Statistical Analysis:

Exploration:

For the Exploration phase, qualitative data will be collected to assess device usability, device comfort, and ease of donning/doffing. There is no formal statistical analysis plan as this phase is only preparatory for Experiments 1 and 2.

Experiment 1:

For Experiment 1, RM-ANOVA will be used to compare our outcome measures between each RAAD condition and unassisted therapy. A "clinically-relevant" improvement will be defined as an improvement of 10%, or more, over baseline for each outcome measure. Cohen's d will be used to calculate effect size.[17] To account for sex as a biological variable, we will recruit an equal number of males and females, matched by GMFCS and age within 2-years. We will use a generalized linear model to determine if participant characteristics and delivery any potential interactions mode (assistance vs. resistance) significantly contribute to our outcome measures.

Experiment 2:

For Experiment 2, RM-ANOVA will be used to compare the change in our outcome measures across assessments. Additionally, a generalized linear model will be used to determine the participant characteristics that significantly contribute to our outcome measures (e.g., sex, age, spasticity, gender, height, GMFCS level), and any potential interactions with delivery mode (assistance vs PT-guided resistance vs PT-&-parent-guided resistance). Similar to the other Experiment, to account for sex as a biological variable, we will recruit an equal number of males and females within each GMFCS level, matched by age within 2-years, and include sex in the generalized linear model. Cohen's d will be used to calculate effect size.[17]

15.4 Data Integrity:

Data integrity and quality control will primarily be done by the site principal investigator (PI Schwartz) and the prime site/sponsor (BiOMOTUM, Inc.) through periodic review. Data will also be reviewed through routine monitoring by the Gillette internal monitoring program or similar.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ **I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research. The stand alone HIPAA Authorization will be used.**

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research: N/A

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ **I will collect information directly from research participants.**

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☒ **Other. Describe: Information will be collected from the Gillette medical record. LAR will sign a HIPAA Authorization as part of this research allowing study team members to access the participant's medical record.**

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

Only the records of participants that have signed the consent form and HIPAA Authorization will be used for data collection and analysis associated with this research. Oversight of this will primarily be done by the site PI (PI Schwartz). All study team members will have been appropriately trained on HIPAA practices, obtaining authorization, and any related requirements prior to any participant interaction and research activities.

16.4 Approximate number of records required for review:

N/A

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ **Communication with research participants will take place outside of treatment settings.**

Communication with potential and enrolled participants will be done via phone, email, and/or in-person. This will be outside the context of standard of care treatment, and may include inquiring about study interest, reminding of upcoming appointments, or contacting for follow-up after participation.

16.6 Explain how the research team has legitimate access to patients/potential participants

All study team members at Gillette have access to the Gillette medical record as a function of their job duties. Participants will be told that their PHI will be used for this research, and a LAR will be asked to sign a HIPAA Authorization before research participation.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In OnCore (oncore.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☒ Other. Describe:

In addition to the above methods, data will be collected, stored, processed, and shared within secure Gillette shared internal networks and on password protected computers. Research data and activities include, but are not limited to, information outlined in sections 6.1 and 6.2.

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as a tablet or smartphone not previously listed

16.8 Consultants. Vendors. Third Parties.

N/A

16.9 Links to identifiable data:

A study ID will be assigned to participants as they are enrolled. This will be linked to the identified data. Identifiers will remain on the data until all data analyses are complete and the study is closed with the IRB, at which time the key will be destroyed following institutional practices. After the study is complete, research records will be stored long-term following institutional practices, and de-identified information will be retained and preserved indefinitely. If required, de-identified data may be saved or shared in a publicly accessible manner.

16.10 Sharing of Data with Research Team Members:

Study team members at Gillette and collaborators will have access to the data collected as part of this research. Study team members at Gillette will share data internally through secure Gillette shared internal networks on password protected computers. Identifiable information shared with collaborators will be shared using secure and HIPAA-compliant methods such as encrypted email and UMN Box.

16.11 Storage and Disposal of Paper Documents:

Hard copy forms will be stored in locked offices/file cabinets at Gillette. When the study is complete, hard copy documents will be stored following standard regulatory practices on and offsite. When that period has expired, hard copy forms will be destroyed following standard institutional practices.

17.0 Confidentiality

17.1 Data Security:

All study team members will be appropriately trained, and training will be documented prior to any participant activity and data collection. Research data will be stored, shared, and accessed using secure methods to ensure data security.

Relevant research data will be stored in research records and Gillette Center for Gait and Motion Analysis database, similarly to how data are stored and processed for standard of care at Gillette.

Additionally, all research activities are covered under a certificate of confidentiality. Appropriate language describing the protections provided by the certificate will be added to the consent form.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data safety and integrity Monitoring:

This study is no greater than minimal risk. Therefore, the site PI (PI Schwartz) and prime site/sponsor (BiOMOTUM, Inc.) will be responsible for monitoring data integrity and will periodically check data collection, entry, adverse events, and study progress. Data will also be reviewed through regular and routine monitoring through the Gillette internal monitoring program or similar, and all activities will follow abbreviated IDE requirements.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

All research data and analyses will be stored on password-protected computers, within secure Gillette shared internal networks, and shared with collaborators using secure methods as previously described. Study team members have been trained on institutional data security, HIPAA regulations, and appropriate computer use.

Research records will be maintained at Gillette for the duration of the study and until the study is closed with the IRB. The site PI (PI Schwartz) at Gillette will primarily be responsible for managing the data collected at Gillette.

19.2 Access to Participants*:*

Participants' parent/guardian will be informed about researchers' need to access their child's medical record for the purpose of this study and will be asked to sign a HIPAA Authorization. They will be told that participation is voluntary.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

In the event that the research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the participant's insurance company. If they think that they have suffered a research related injury, they will let study team members know right away.

20.2 Contract Language:

N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Gillette study team members that are trained and delegated will obtain informed consent in-person and in a private setting at Gillette.

The LAR will be asked to sign a consent form for each phase the participant will complete (e.g., Exploration and/or Experimental). Participants 8 to 17 years old with no or mild cognitive impairment will be asked to sign an assent form. If a participant is unable to sign an assent form due to cognitive or physical abilities, verbal assent (e.g., physical or verbal cues) will be obtained and documented as appropriate. If the LAR indicates that the child has more than mild cognitive delays, assent will not be obtained and will be documented as appropriate. A comment of study participation will be made in the participants medical record as communication with other hospital staff.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

N/A

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

N/A

21.4 Non-English-Speaking Participants:

N/A

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

We will use the Gillette medical record to extract date of birth to determine that potential participants qualify.

Further, informed consent will only be obtained from one LAR because the study constitutes no greater than minimal risk.

There is no regulation on the exact age at which a child is required to complete a written assent. For our study, we have chosen to consent children (with no or mild cognitive impairment) who are ages 8 to 17 years old and should be able to understand the relatively simple study activities. If a participant can write, written assent will be obtained. If not, physical or verbal cues will be documented as assent when possible and appropriate. If the LAR indicates that the child has more than mild cognitive delays, assent will not be obtained and will be documented as appropriate.

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

N/A

21.7 Adults Unable to Consent:

N/A

22.0 Setting

22.1 Research Sites:

Gillette is one of 3 collaborative sites which include Northern Arizona University and Shirly Ryan Ability lab and overseen by the prime site/sponsor BiOMOTUM, Inc.

The site PI (PI Schwartz) will lead all activities conducted at Gillette and outlined in this protocol.

22.2 International Research:

N/A

23.0 Multi-Site Research

23.1 Study-Wide Number of Participants:

Up to 86 participants will be recruited study-wide (12 from Northern Arizona University, 24 from Shirley Ryan Ability lab, and 50 from Gillette)

23.2 Study-Wide Recruitment Methods:

Norther Arizona University will be recruiting participants in Aim 1 and Shirley Ryan Ability Lab will be recruiting participants in Aim 2 using standard institutional methods. These activities are covered by separate IRB protocols and are not described here.

Gillette will be recruiting participants for Aim 3 using methods described above. The site PI (PI Schwartz) will be responsible for these activities.

23.3 Study-Wide Recruitment Materials:

N/A – Each institution is responsible for their own recruitment materials.

Materials for the activities completed at Gillette are included with this submission.

23.4 Communication Among Sites:

This collaborative study will be run by the lead investigator Dr. Raymond Browning CEO of BiOMOTUM, Inc. and Dr. Zachary Lerner at Norther Arizona University and BiOMOTUM, Inc. Dr. Michael Schwartz is co-investigator on the award and will act as the Gillette site PI.

Study sites participate in regular video conferences, which will continue throughout the study duration.

Web-based and in-person trainings between sites will occur as time and schedules permit. This training will be documented, and data collection will not occur until all study team members are appropriately trained on the study protocol. Study monitoring of Gillette activities will be conducted through the Gillette internal monitoring program or similar. Non-compliance and reportable events will be reported following federal regulation, as necessary.

23.5 Communication to Sites:

Problems and interim results will be communicated during regular video conferences or additional electronic and telephonic communication, as necessary. Non-compliance and reportable events will be reported following federal regulation, as necessary.

24.0 Coordinating Center Research

N/A

25.0 Resources Available

25.1 Resources Available:

Gillette is positioned to contribute to successful completion of this proposed project because of its one-of-a-kind comprehensive, integrated team approach to the treatment of individuals with CP. Specifically, this study will make use of the Gillette Center for Gait and Motion Analysis. Study participants will be recruited from the Gillette population, which sees over 2,000 children and adolescents with CP annually. This represents one of the largest pools of patients with CP in the nation and will ensure adequate recruitment of participants for the proposed study.

26.0 References

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