PROTOCOL COVER SHEET

TITLE: Arm Motor Rehabilitation, Entertainment and Cognition System for the Elderly

PROTOCOL ID: 10-001

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RESEARCH SITES:

- Bright Cloud International Corp, CCIT Suite B203, 675, US Hwy 1, North Brunswick, NJ 08902 (clinical site for BrightArm Compact -BAC usability study, and feasibility pilot study of individuals with Parkinson's Disease using BrightBrainer BBX);
- PowerBack Rehabilitation (clinical site for BrightArm Compact feasibility study on inpatients early sub-acute post stroke);
- Kessler Foundation, 1199 Pleasant Valley Way, West Orange, NJ 07052-1424 (Clinical site for BAC randomized controlled study).
- Hundal Neuropsychology Group LLC, 121 Flanders Drive, Hillsborough, NJ 08844 (performs cognitive evaluations at PowerBack Rehabilitation)
- Data Driven Innovation 21 Bishop Ave. Westhampton, NY 11977- 1613 (performs bio-statistical data analysis)
- Team Design Group (where BAC prototypes were manufactured according to Bright Cloud International designs – no human subjects).

I. **Purpose of the study and background**

Purpose of the study: The research has the following aims:

1) to develop the (BAC), a game-based upper-extremity motor and cognitive rehabilitation system using virtual reality simulations;
2) To do a usability study by healthy elderly age matched volunteers.
3) To do a feasibility evaluation on participants who are stroke survivors in the early sub-acute phase inpatients at short term Post-Acute rehabilitation facility;
4) To do a small pilot feasibility study on individuals with Parkinson's disease using BrightBrainer BBX system at Bright Cloud International CCIT site for upper body and cognitive training.
5) To do a randomised controlled study of the BAC experimental system on elderly subjects (50 to 80 years old) who had a stroke recently (more than 5 days prior to

participation), thus are in the early sub-acute phase post-stroke and who may suffer from cognitive impairments.

The feasibility pilot on individuals with PD at BCI Laboratories (CCIT) will determine technology acceptance and possible clinical benefit for better arms/hands motor control (reduced tremor), as well as focusing. Results from this pilot will be the basis for a follow up larger study.

The BAC usability component will take place at Bright Cloud International Laboratories, CCIT (North Brunswick, NJ). It will generate data on ease of use of the system, technical issues , and may lead to software improvements;

The BAC feasibility study will take place at PowerBack in Piscataway, NJ and will give initial indication of technology acceptance, as well as clinical benefit in terms of improved motor and cognitive function, reduced upper body pain, as well as diminished depression (feasibility) of short term residents at a Post-Acute facility.

The randomised controlled trials will take place at Kessler Foundation (West Orange, NJ). It will develop a new longitudinal therapy for elderly stroke survivors who are inpatients and then outpatients at a regional rehabilitation hospital, by adding BAC training to customary care for both inpatients and outpatients. Two systems will be used, improving continuity of care (one each for inpatient and outpatient settings).

This Protocol has **split oversight**, with the usability and feasibility components being overseen by WIRB, and the RCT component being overseen by Kessler IRB (KIRB).

1. **Background:** Patients who are in the chronic phase (> 9 mo) post stroke have been shown to improve if they train intensively and for long duration. This rehabilitation needs to be done in a task-oriented way, provide knowledge of performance to the patient, while making sure the patient is focusing on the exercise. Patients who are in the sub-acute phase post-stroke (< 6 months from the event) have weaker arms, and typically receive less upper extremity training. This is especially true in the early sub-acute phase (5+days after CVA) when the brain exhibits hyper plasticity. These patients could benefit from a system such as BAC, which modulates gravity bearing on the affected arm. At the same time they may benefit from neural rewiring or brain plasticity that is induced by a large number of task-oriented arm repetitions. The Principal Investigator, Dr. Nam Kim, has conducted pilot studies of advanced rehabilitation technology on several patient populations over the past 10+ years. In his previous capacity as Post-Doctoral Fellow at Kessler Foundation (the same clinical site we will use) and Research Associate at Rutgers Biomedical Engineering Department, he developed a novel rehabilitation device for stroke patients and conducted a clinical research to assess and improve visuo-motor targeting function which translated to activities of daily living (ADLs). At Bright Cloud International Dr. Kim is overseeing several studies involving the type of custom virtual rehabilitation games that will be developed for the patient population in the current study.

Prior research at BCI implemented a training technique that consisted of exercises in the form of games played with the affected arm, while supported by a low friction table, and controlling a hand avatar shown on a large display. Gradually the table was manually tilted, and exercises increased in difficulty. Each patient was evaluated for motor function and transfer to improved independence in ADLs. These evaluations were done by a senior occupational therapist, pre-study, post-study and at 4 to 6 weeks follow-up. Results were positive in terms of improved arm reach, improved arm and hand strength and motor coordination, larger active range of movement for shoulder, arm and fingers, and more independence in ADLs. The BAC is a follow up to the BrightArm Duo system (approved by WIRB for use on subjects sub-acute and chronic post-stroke). It uses similar therapeutic games, involving movement of both arms, and a similar but smaller low friction table. The arm movement, grasp strength, finger extension are detected by a trackers and the new BrightBrainer Grasp game controller (developed under WIRB Protocol 16-001) and transmitted to the computer running the session. Results using the BrightArm Duo showed benefits in the cognitive domain on elderly nursing home residents at Roosevelt Care Center [House G, G. Burdea, K. Polistico, D. Roll, J. Kim, F. Damiani MD, S. Keeler, J. Hundal, S. Pollack. Integrative rehabilitation of stroke survivors in Skilled Nursing Facilities: the design and evaluation of the BrightArm Duo. *Disability and Rehabilitation-Assistive Technology*. November 2016. 11(8):683-94].

Similar to the population targeted by this amendment, the BrightArm Duo was part of a small pilot study where an experimental group of inpatients early sub-acute post stroke trained on the BrightArm Duo for 4 weeks (3 sessions/week) in addition to customary care. When compared to controls who were patients at the same facility, but had only customary care, the experimental group showed improvements in range of motion, task completion time, and teamwork play. Results were published in [House G, G. Burdea, K. Polistico, N. Grampurohit, F. Damiani MD, S. Keeler, J. Hundal, S. Pollack. A rehabilitation first – nursing home tournament between teams of chronic post-stroke residents. *Games for Health.* February 2016. 5(1), 75-83.], and many other peer-reviewed journals.

While BrightArm Duo proved quite beneficial to patients, clinicians considered it too large for actual clinic use. The cost of the system was also a factor for its non-adoption in clinical sites. As a consequence, BCI has applied for and obtained further funding from NIH, to develop BAC. It is about half the size of its BrightArm Duo precursor, and a simplified architecture (that will reduce cost). The smaller and cheaper BAC (Figure 1) does not however short-change the patient. On the contrary, it integrates better tracking (replacing overhead expensive cameras with wireless VIVE tracker. More importantly, the novel hand controllers used to play BCI therapeutic games now also measure finger extension, as well as forearm pronation/supination.

Figure 1 BAC rehabilitation table: a) prototype at BCI Laboratories (CCIT); b) BBG controller measuring position, grasp strength, finger extension and pronation/supination.

The BrightBrainer is a Class I medical device (listed with the FDA). It is a compact, mobile platform that currently is the subjects of Protocol 16-001 for home telerehabilitation of subjects chronic post-stroke living at home.

In the pilot feasibility study on individuals with PD, we will use the BrightBrainer (Figure 2) to attempt to reduce arm tremors and improve error rates and completion times in virtual reality tasks.

Figure 2. BrightBrainer system to be used in the pilot feasibility for individuals with PD

i. Why is this study being done?

The research project is intended to provide information pertaining to the usability, feasibility and clinical benefit of the *BAC* system for early sub-acute post CVA rehabilitation, improved cognition and emotive state while inpatient in short-term care facility settings (PowerBack Rehabilitation), in acute inpatient rehabilitation settings (Kessler Foundation) and in an outpatient clinic at the same research hospital. Specific aims are:

- BAC technology acceptance (all groups);
- improved motor function for upper extremity;
- strengthening shoulder and fingers
- increased range of motion for arms and fingers;
- improved independence in activities of daily living;
- improved cognition;
- improved emotive state;
- reduction in perceived upper body pain.

This study targets participants, who had suffered a stroke very recently, who may or may not have been diagnosed with mild cognitive impairments or dementia (including Alzheimer's disease). It is important to find out if these improvements can be obtained with the computer game-based integrative (motor-cognitive) bimanual rehabilitation developed by Bright Cloud International Corp, and if these gains transfer to daily activities. The study also aims at determining benefit of continuum care training on the BAC in addition to conventional rehabilitation for participants who are inpatients and then outpatients at a rehabilitation hospital and clinic.

Another component of the research project is a small pilot targeting individuals with Parkinson's disease. For them the project is going to:

- determine technology acceptance when using the BrightBrainer system;
- benefit to arms motor function and strengthening when playing BCI therapeutic games;
- benefit to reduction or tremor when playing games;
- cognitive benefits
- improvement in their wellbeing.

ii. **Criteria for Subject Selection**

<u>For the BAC study on subjects early sub-acute post stroke</u>

o **Number of subjects:** We expect to enrol up to 50 subjects. Of these 4 will be healthy age-matched volunteers, 6 will be stroke survivors being treated at PowerBack, 20 stroke patients at Kessler Foundation, and 20 will be spouses/caregivers of subjects participating in the randomized control trials component of this study.

o **Gender of Subjects.** Both male and female subjects will be equally enrolled. While the majority of the population is female, owing to the gender statistics for the age group targeted (>50 to 80 years old), since we will also recruit spouses/caregivers we expect an equal gender distribution. Due to their age, we do not anticipate any pregnant female to participate.

o **Age of Subjects.**

Age between 50 and 80. Subjects targeted are either: 1) healthy volunteers at BCI/CCIT location; inpatients in PowerBack Rehabilitation sub-acute post-stroke; 2) inpatients and then outpatients at a research hospital and its outpatient clinic at Kessler Foundation.

o **Racial and Ethnic Origin.**

No exclusions will be made due to race or ethnic background. According to the US Census Bureau [US Census Bureau, 2010] the Bergen County region of New Jersey, where Kessler Rehabilitation Institute and the outpatient Clinic are located, is made up of approximately 74% white, 16% Asians and 7% African Americans with 3% being other races. Persons of Hispanic or Latino origins represent about 16% of the Bergen County population. It is reasonable to expect similar groupings for the subjects of this investigation. If it appears that participation according to gender or race is going to be different than that of the Census data, we will actively recruit additional subjects to achieve that distribution. There is no reason to expect any differences in the results of this investigation as a consequence of race or of ethnic background.

o **Inclusion Criteria (general)**

- Age 50 to 80;
- Healthy age-matched volunteers
- diagnosis of CVA that occurred more than 5 days prior (for the stroke survivors group);
- English speakers;
- UE unilateral or bilateral involvement (from new bilateral CVA)
- motor involvement (FMA score 20 to 45);
- ability to actively move UE more than 10^{o} for shoulder and elbow flexion/extension;
- ability to actively extend fingers at least 5^{o}
- cognitive skills to participate (Montreal Cognitive Assessment (MoCA) [Nasreddine et al 2005] score 10-30).
- The adaptive nature of BBC system hardware and therapeutic games can compensate for the motor limitations due to other co-morbidities. Therefore potential participants will not be excluded due to co-morbidities such as Parkinson or arthritis. Subjects may have normal cognition, MCI or dementia, since the games can compensate for diminished cognition through built-in cues and instructions.

o **Inclusion Criterion for the controlled clinical trials arm at Kessler Foundation**

- Living within 25 miles radius of Kessler Foundation West Orange location. This will facilitate participation in the outpatient clinic training, which follows inpatient rehabilitation.

o **Exclusion Criteria. (general)**

- being younger than 50 or older than 80 years of age
- previous stroke
- Inability to actively extend fingers at least 5 degrees;
- Fugl-Meyer scores of 19 or less;

- severe visual neglect or legally blind
- severe hearing loss or deafness
- receptive aphasia or severe expressive aphasia;
- severe spasticity (Modified Ashworth Scale 4/4)
- contractures of the upper limb joints
- uncontrolled hypertension (>190/100 mmHg)
- severe cognitive impairment determined by Montreal Cognitive Assessment (MoCA) [Nasreddine et al, 2005] test of 9 and below;
- No chemodenervation or nerve block to upper limb involved during the experimental period (e.g., botulinum toxin injection)
- inability to speak English;
- a history of violence or drug abuse.
- inability participate in the neuropsychological pre-study assessment for reliable scores (e.g., cognitive impairment, communication disorders).

- **Exclusion Criteria. (Controlled study arm)**
- Those living outside approximately 25 miles radius of Kessler Foundation West Orange location. Those living too far will have a harder time completing the study as outpatients, as they will probably choose clinics closer to home.

- o **Vulnerable Subjects.** The targeted subjects for the feasibility arm of the study will be sub-acute phase patients at PowerBack. Those targeted from the controlled trials arm of this study will be inpatients in a rehabilitation facility who subsequently become outpatients at a local research hospital and its outpatient clinic. We expect that the majority of participants early post-stroke will be using wheelchairs for mobility. As such we have designed the equipment they will use to be wheelchair accessible, without requiring transfers. This improves safety and comfort. An occupational therapist will be in the room with the participant during rehabilitation on BAC, to assist as needed. Subjects will not be coerced into participation. The games adapt automatically to each patient's ability and functional level, thus participants will not be at increased risk. They will practice their arms while sitting and their arms will be initially supported during game play when training on the BAC. Biosensors (measuring skin conductance and pulse) will give independent indication of participant's level of stress. Games played by participants will be gradated over the duration of rehabilitation.

<u>For the BrightBrainer study on subjects with Parkinson's Disease</u>

o **Number of subjects:** We expect to enrol 2 subjects. They will be living in the community.
o **Gender of Subjects.** We will aim to recruit a male and a female subjects. Due to their age, we do not anticipate a pregnant female to participate.
o **Age of Subjects.** Age between 50 and 80.
o **Racial and Ethnic Origin.** No exclusions will be made due to race or ethnic background.
o **Inclusion Criteria (general)**

- Age 50 to 80;
- diagnosis of Parkinson's Disease that occurred more than 6 months prior

- English speakers
- Able to safely get in and out of chair
- Living within 25 miles radius of BCI location so to facilitate participation
- Hoehn and Yahr stage of Parkinson Disease I-III

o **Exclusion Criteria.**

- being younger than 50 or older than 80 years of age
- severe visual neglect or legally blind
- severe hearing loss or deafness
- receptive aphasia or severe expressive aphasia;
- severe spasticity (Modified Ashworth Scale 4/4)
- contractures of the upper limb joints
- uncontrolled hypertension (>190/100 mmHg)
- severe cognitive impairment determined by Montreal Cognitive Assessment (MoCA) [Nasreddine et al, 2005] test of 17 and below
- inability to speak English;
- a history of violence or drug abuse.
- any surgical procedures for PD such as deep brain stimulators will be cause for exclusion.

iii. **Methods and Procedures**

Usability Evaluation (BCI Laboratories at CCIT)

Subsequent to IRB approvals from Western IRB (for BCI) and Kessler IRB (for Kessler Rehabilitation Institute/Kessler Foundation) we will commence subject recruitment. We will start with 4 age-matched elderly healthy volunteers (male and female) with preference to those with no computer games experience. 2 volunteers will each perform usability sessions (2 times per week) in the first 2 weeks. They will be instructed to move the “involved” arm over a limited range and grasp lightly, so to mimic the assumed functionality of elderly in the sub-acute phase post-CVA. They will also be instructed to extend fingers a little. Each session volunteers will fill in the USE standardised usability questionnaire [Lund 2001]. This questionnaire will rate the usefulness, ease of use, ease of learning, and satisfaction with the BAC system.. In addition, after each session the volunteers will fill a custom rating questionnaire, with more specific questions than the general USE form. The custom usability form will solicit comments on specific games instructions, ergonomic issues with the robotic table, with donning and doffing the BBG hand controllers, and degree of assistance needed in doing so, as well as general comments for improvement. Volunteers will receive a $25 money order at the completion of each usability evaluation.

Sessions will be interspaced with days when the programmer and engineer will address issues uncovered in the previous session(s). The process will be repeated in the subsequent 2 weeks with the other 2 volunteers. The Usability study will inform improvements necessary in the BAC system prior to feasibility study.

Feasibility Study (PowerBack Rehabilitation)

This will be an ABA protocol, with measures taken pre- (A), during experimental therapy (B) and post-intervention (A).

Participants Recruitment

6 elderly sub-acute post-CVA admitted to PowerBack for inpatient rehabilitation will be recruited. Participants will be pre-screened through a script questionnaire and MoCA screening. Those who met inclusion criteria will be consented by Jonathan Tapia OT (Co-Investigator and Director of Rehabilitation at PowerBack).

Participants standardised evaluations for feasibility study

Before the VR training (A) all participants will be evaluated by a senior occupational therapist (OT). The OT will evaluate:

- UE FMA,
- Jebsen test of hand function [Jebsen 1969],
- bimanual activities CAHAI-9) [Barreca 2004]),
- UE active range of shoulder movement - goniometer,
- shoulder strength -wrist weights,
- grasp and pinch strength -dynamometer and pinch meter), and
- independence in ADLs (upper extremity functional index [Stratford et al, 2001]).
- Blood Pressure and Pulse.

Pre-experimental therapy, a neuropsychologist, blinded to the intervention, will perform the cognitive/emotive evaluations. We will assess:

- emotive state (via the Beck Depression Inventory II),
- verbal and visual attention (with the Neuropsychological Assessment Battery NAB),
- processing speed (with the Trail Making Test A [Heaton 1991] - TMT),
- verbal and visual learning and memory (with the Hopkins Verbal Learning Test, Revised (HVLT-R) [Brandt 2001] and the Brief Visuo-spatial Memory Test, Revised (BVMT-R) [Benedict 1997]), and
- executive function with the Trail Making Test B (TMT-B) and the NAB Executive Functioning Module.

The initial evaluations will serve as baseline for all participants. Subsequent to the VR training on the BAC system, all feasibility participants will be evaluated again (A) for motor impairments and function, cognitive and emotive state for indication of clinical benefit. These clinical evaluations will be performed at the PowerBack.

Inpatient experimental therapy for the feasibility study

The first BAC system will be installed at PowerBack and 6 participants 5 to 10 days post CVA admitted to inpatient rehabilitation will be recruited. They will train for up to 3 weeks, every other day, totalling up to 12 rehabilitation session playing a series of integrative exercises. Each session will start with a baseline for arm reach in the horizontal and vertical plane, pronation/supination range, as well as grasp strength and finger extension. These baselines will be used to adapt each game to an individual participant's motor impairment level in a given day, making the games winnable. Games

will produce congratulatory feedback, designed to maximize motivation, giving the subjects a feeling of control over their therapy and of accomplishment.

To combat boredom, new games will be added, such that the number of available games will progress from 4 games for sessions 1-4 to 6 games for sessions 5-8, and 8 games for sessions 9-12. The characteristics of each game will change from week to week (for example later-stage games will use dual-tasking involving moving and grasping simultaneously). Subjects will have a choice of games to play from among those available and will know the level they had achieved in a particular game.

The VR training will progress from 15 minutes/session of actual play (sessions 1-4), to 20 minutes (sessions 5-8) to 30 minutes (sessions 9-12). The BAC will be used in uni-manual mode providing training to the affected UE in sessions 1-4, and in bimanual mode for sessions 5-12. Furthermore, grasp and shoulder training will progress from no grasping required in sessions 1-4, to momentary grasping needed to play in sessions 5-12. Towards the end of training each session should induce >600 repetitions/arm, an amount consistent with inducing brain plasticity [Nudo 1997]. Subjects will play while supported by the BAC table in horizontal position. At the discretion of the therapist in the room, if moderate to mildly impaired participants tolerate, the table may be tilted up to 10 degrees.

Before the start of a session the participant's blood pressure and pulse will be measured, to make sure it is safe to train that day. After the half-time mark is reached, the BAC system will automatically pause the session and ask for another reading of blood pressure and pulse. Once the prescribed game time is reached for a session, the game time is automatically ended by the system and the Therapist prompted to do one more blood pressure and pulse readings.

A remote database will store game performance data and allow access by the researchers following subject compliance to protocol and game performance progression. Subjects will be given the opportunity to make up any missed sessions.

At the end of sessions 4, 8 and 12 subjects will fill online subjective evaluation form rating their experience on the system. When logged over time these evaluations will give a measure of the subject's perceived value of the experience. Technology acceptance will also be gaged based on adherence to protocol.

At the end of Session 12 of a given subject, the OT will fill his/her custom evaluation form of the BAC system. The therapist will rate the ease of setting up sessions, the perceived benefit in terms of reduced work load, ease of notes entering, number of technical problems encountered, appropriateness of training intensity and overall satisfaction. Therapists will also have a log-book for noting session specific issues. Participants in the feasibility evaluation will not be paid.

Subsequent to the training of the 6 subjects at PowerBack, and based on their feedback we may fine-tune the BAC systems prior to deployment to the Kessler Foundation for the randomized control study.

Outcomes of feasibility study on individuals early post-stroke

Primary outcomes:

- The main motor outcome measure will be the FMA UE score, and success will be a group average score increase of 10 points or more, compared to baseline.
- The main outcome for the cognitive domain will be executive function improvement measured by Trail Making Test B (TMT-B) and the NAB Executive Functioning Module.

Secondary outcomes:
In the motor impairment domain secondary outcomes will be:

- increased arm range in pronation/supination (based on new games we will develop);
- grasp strength increase;
- finger extension range increase,
- increase in UEFI;
- bimanual training to improve CAHAI 9 scores (by at least 6 points), reflecting more ADL independence in tasks that are requiring both arms. The progression in ADL independence will be indicative of transfer to function.
- Other secondary outcomes will be changes in therapeutic game scores,
- change in game duration (indicative of reduction in task completion time)
- change in play intensity (number of arm movement repetitions/minute);
- participants' subjective evaluation scores for ease of use of the BAC, and overall system rating.

In the cognitive domain, secondary outcomes will be:

- improved focus,

better verbal and visual memory.
In the emotional domain, we will evaluate the depression scores as measured by the Becks Depression Inventory II standardized test. We will consider success an average group reduction of 5 points in the severity of depression.

Pilot Feasibility Study for BrightBrainer use by individuals with PD (BCI/CCIT site)

This will be an ABA protocol. Measures will be taken pre- outpatient therapy (A), during outpatient experimental therapy on BrightBrainer (B), and post inpatient therapy (A).

Subject Recruitment
Namrata Grampurohit OT will reach out to PD support groups in NJ to publicize the pilot. She will use the publicity flier developed for this purpose. Those interested will be consented at CCIT.

Subject standardised evaluations for pilot feasibility study on individuals with PD.

- the Canadian Occupational Performance Measure (Law et al., 2005)
- the Upper Extremity (UE) dual task function test. UE dual task function test involves repeated upper extremity elbow flexion with a gyroscope to measure repetitions and angular velocity with an added cognitive task such as counting backwards by seven or counting months of the year backwards (Toosizadeh et al., 2016)
- Timed Up and Go Cognitive (Shumway-Cook, Brauer, & Woollacott, 2000),
- cognitive measures of Trail making test (Reitan & Wolfson, 1994)

- Stroop test (Hsieh, Chen, Wang, & Lai, 2008).
- Upper extremity specific measures of Nine Hole Peg Test (Mathiowetz & Kashman, 1985)
- Modified functional reach test (Smithson, Morris, & Iansek, 1998),
- Parkinson's Disease Activities of Daily Living Scale (Hobson, Edwards, & Meara, 2001) and

Movement Disorder Society Unified Parkinson's Disease Rating Scale (Goetz et al., 2007)

Outpatient experimental therapy for individuals with PD

Two subjects will do 12 sessions over 4 weeks at CCIT, playing the same therapeutic games previously described. Session duration and progression will be same. An additional variable will be arm tremor (in terms of magnitude and frequency).

Two new baselines will be added, to determine tremor for each arm and for the index finger. The baselines will be done before each session and will use the BrightBrainer VIVE game controllers. The frequency of data sampling from these controllers is sufficient to measure the hand and index finger tremor and will inform game sensitivity parameters.

PD pilot study Outcomes

Primary outcomes

The primary outcomes will include Canadian Occupational Performance Measure (Law et al., 2005) and Upper Extremity (UE) dual task function test. UE dual task function test involves repeated upper extremity elbow flexion with a gyroscope to measure repetitions and angular velocity with an added cognitive task such as counting backwards by seven or counting months of the year backwards (Toosizadeh et al., 2016)

Secondary outcomes

The secondary outcomes will include another dual task measure of lower extremity Timed Up and Go Cognitive (Shumway-Cook, Brauer, & Woollacott, 2000), cognitive measures of Trail making test (Reitan & Wolfson, 1994) and Stroop test (Hsieh, Chen, Wang, & Lai, 2008). Upper extremity specific measures of Nine Hole Peg Test (Mathiowetz & Kashman, 1985) and Modified functional reach test (Smithson, Morris, & Iansek, 1998), and two PD specific scales of Parkinson's Disease Activities of Daily Living Scale (Hobson, Edwards, & Meara, 2001) and Movement Disorder Society Unified Parkinson's Disease Rating Scale (Goetz et al., 2007)

Other secondary outcomes will be changes in therapeutic game scores, change in game duration (indicative of reduction in task completion time) and change in play intensity (number of arm movement repetitions/minute). Another secondary outcome will be subjective evaluation scores for ease of use of the BrightBrainer, and overall system rating using System Usability Scale.

Randomized control study protocol (Kessler Foundation IRB Oversight)

This will be an ABA (A)BA protocol. Measures will be taken pre- inpatient therapy (A), during inpatient experimental therapy on BAC (B), , post inpatient therapy (A). After discharge, measurements will again be taken pre- outpatient therapy (A) if outpatient therapy is not started immediately after inpatient therapy. All subjects will have

measures taken during outpatient therapy on BAC (B), and post-outpatient treatment (A).

Subject Recruitment

20 elderly 5 days or more post-CVA admitted to Kessler Institute for Rehabilitation/Kessler Foundation) for inpatient rehabilitation will be recruited. Subjects will be pre-screened through a standardized questionnaire and MoCA screening. We expect to screen at least 70 potential subjects, also trying to determine candidates who will continue outpatient rehabilitation at Kessler Foundation. Those who met inclusion criteria will be consented by AM Barrett MD or Dr Phalgun Nori (Co-Investigators). The 20 recruited subjects will subsequently be randomised equally into an experimental group (n=10) and a control group (n=10).

We will also recruit the 20 caregivers of the experimental and control subjects. The caregivers will provide feedback on the subjects during the outpatient component of their therapy, every 4 weeks. We will be looking for changes in independence in activities of daily living, cognition and mood that the caregivers will report, as well as self-reported outcomes by the subjects. The feedback will be using the Stroke Impact Scale [Duncan et al. 2002] and the Upper Extremity Functional Index (UEFI) [Stratford 2001] standardized questionnaires, as well as free form communication with researchers.

Subject standardised evaluations for control study on early sub-acute post stroke

Both experimental and control groups will undergo standardised evaluations for motor function/impairment, cognition and emotive states. All subjects will be evaluated before, and after their in-patient rehabilitation. Those patients who transition to home rehabilitation will be evaluated again before commencing outpatient rehabilitation, while those who transition directly to outpatient rehabilitation will not. All subjects will be evaluated again at the completion of their outpatient therapy. All clinical evaluations of the control study subjects will be performed at the Kessler Kessler Foundation.

OT evaluations

An occupational therapist blinded to the treatment allocation will evaluate for motor impairment and function of both UEs. These evaluations are the following:

- Fugl Meyer Assessment (FMA)
- Jebsen test of hand function [Jebsen 1969]
- active range of shoulder, elbow and finger movement (goniometer)
- shoulder strength (wrist weights)
- range of forearm pronation/supination
- grasp strength (dynamometer)
- pinch strength (pinch-meter)bimanual activities (Chedoke Inventory -9) [Barreca 2000]. The need to evaluate both UEs stems from the nature of BAC bimanual training and from our inclusion of subjects who may be bilaterally affected by their first CVA.

Emotional & Neuropsychological evaluations

The neuropsychologist will perform the cognitive/emotive evaluations. We will assess

- emotive state (via the Beck Depression Inventory II)
- verbal and visual attention (with the Neuropsychological Assessment Battery NAB)
- processing speed (with the Trail Making Test A [Heaton 1991] - TMT)
- verbal and visual learning and memory (with the Hopkins Verbal Learning Test, Revised (HVLT-R) [Brandt 2001]
- Brief Visuo-spatial Memory Test, Revised (BVMT-R) [Benedict 1997])
- executive function with the Trail Making Test B (TMT-B) and the NAB Executive Functioning Module.

The initial evaluations will serve as baseline for all participants. Subsequent to the inpatient VR training, all participants will be evaluated again for cognitive and emotive state for indication of clinical benefit. Subjects who transition to home will be evaluated again at the start of their outpatient rehabilitation. All subjects will be evaluated again for cognitive and emotive state at the end of their outpatient therapy. For subjects who skip home rehabilitation and transition directly to outpatient training, the measures at discharged from inpatient rehabilitation will be considered as baseline for start of outpatient training. To minimize test learning effects we will use alternate test forms for NAB tests, as well as reliable change formulas for all other forms [Jacobsen and Truax, 1991].

Inpatient and outpatient experimental therapy for the control study at Kessler Foundation

All subjects, regardless of group randomisation, will continue their standard of care rehabilitation (physical therapy, occupational therapy, speech and language therapy and cognitive training). All subjects, regardless of randomization, will have the same duration of therapy. Specifically, subjects randomised in the control group will have an added duration of standard of care rehabilitation equal to the experimental group training duration on the BAC.

Experimental group

10 subjects in the experimental group will be trained on the BAC system in addition to their standard of care intervention. Sessions will consist of a series of non-repeating custom and adaptable integrative games played while sitting at the robotic table. During the in-patient portion of the experimental therapy they will perform sessions every other day, for up to 3 weeks (12 sessions total). When transitioning to outpatient therapy, they will perform 2 to 3 sessions a week for 2 to 3 months.

Each experimental session will start with baseline measures of supported arm reach, pronation/supination range, finger extension and grasp strength. These measures will be done for the more affected arm during the initial 4 sessions, and for both arms thereafter, since therapy will progress to bimanual mode. The length of each session will increase with the progression of therapy, from 15 minutes in the first in-patient therapy session, to 30 minutes during the last in-patient session. Then during outpatient therapy portion, sessions will commence at 30 minutes duration and will progress to 45 minutes of actual game play.

The tilting angle of the robotic table will be used to modulate gravity loading on (typically) weak arms. If the subject is low-functioning the table may be tilted downwards to assist movement away from the trunk. Conversely, as the subject gets stronger, the table will be tilted upwards so to increase gravity loading. We plan on keeping the table flat during the inpatient sub-acute training and envisage this upwards tilting to occur in the outpatient component of the therapy.

Apart from lengthening the sessions and increasing gravity loading through robotic table tilting, we will increase session difficulty by incrementing the difficulty level of individual games. For example we may increase the number of face-down cards to be paired during the *Card Island* game (which trains short term visual and auditory memory), or increase the speed of the ball during *Breakout 3D* game (which trains hand-eye coordination, focusing, and dual tasking). In the outpatient portion, when attempting to lift the arm off the table, the weight of the forearm support will increase training difficulty further.

In the motor domain the session will train endurance (by increasing the length of training), strength (by modulating gravity loading and lifting arm off table), motor control (by requiring patients to follow prescribed paths), and movement speed (by inducing more arm repetitions per minute).

In the cognitive domain the cognitive load will gradually be increased by moving from uni-manual play (need to control only one avatar) to bimanual play (simultaneous control of two avatars). This will train split attention, task sequencing and dual tasking, something problematic for the elderly.

Control group

10 subjects in the control group will receive their standard of care intervention during inpatient rehabilitation post CVA. To this we will add an equal duration of standard of care to the experimental therapy (progressing from 15 minutes/session in sessions 1-4 to 30 minutes during the last inpatient session). In the outpatient period they will have an added duration of customary therapy. The added therapy will progress from 30 minutes/session at start of outpatient therapy to 45 minutes/session at the end, matching the experimental group training duration on the BAC.

Control study Outcomes

Primary outcomes

The primary outcomes for both groups will be those outlines in the Feasibility Study component of the project. The main motor outcome measure will be the FMA UE score, and success will be a group average score increase of 10 points or more, compared to baseline. The main outcome for the cognitive domain will be executive function improvement measured by Trail Making Test B (TMT-B) and the NAB Executive Functioning Module.

Secondary outcomes

The secondary outcomes for both groups will be those outlines in the Feasibility Study component of the project,

In the motor impairment domain, secondary outcomes will be increased arm range in pronation/supination (based on new games we developed), grasp strength increase, finger extension range increase, and increase in UEFI. We expect bimanual training to improve CAHAI 9 scores (by at least 6 points), reflecting more ADL independence in tasks that are requiring both arms. The progression in ADL independence will be indicative of transfer to function. Other secondary outcomes will be changes in therapeutic game scores, change in game duration (indicative of reduction in task completion time) and change in play intensity (number of arm movement repetitions/minute). Another secondary outcome will be subjective evaluation scores for ease of use of the BAC, and overall system rating.

In the cognitive domain, we also foresee the subjects will have improved focus, better verbal and visual memory. In the emotional domain, we will evaluate the depression scores as measured by the Becks Depression Inventory II standardized test. We will consider success and average group reduction of 5 points in the severity of depression.

In addition there will be supplementary secondary outcomes:

a) Scores obtained on the Stroke Impact Scale (Version 3);
b) feedback from the subjects during the outpatient component of therapy (only for intervention group);
c) feedback obtained from caregivers during outpatient therapy. The caregivers for subjects in either experimental or control groups will use the same feedback forms and provide feedback at the same time points.

An additional important outcome will be the rate of motor recovery as visualized by the curves of evaluation variables obtained pre-, and post inpatient therapy, then pre-, and post- outpatient therapy. These will provide indication on the envisaged benefits from the use of the experimental device and elucidate what gains are due to natural recovery and what gains may be attributes to training on the BAC.

o **Data Analysis and Data Monitoring.** We will use repeated measures of ANOVA statistical analysis to look at the participants' data comparing pre-training conventional evaluation results with post-training results, to determine early indications of clinical benefit. We will also collect subjective evaluation questionnaires from each participant and from the occupational therapist (once post-training) on their impression of the system, its perceived benefits and shortcomings, its ease of use in a clinical setting. We will also collect data on Activities of Daily Living, using a standardised form, as well as data from caregivers so to gauge transfer of training to real life activities.

In order to gauge technology acceptance we will collect a subjective evaluation of the BAC from each participant in the experimental group. The scores (1 – least favourable outcome to 5 most favourable one) from each question will be averaged over the group. The BAC subjective evaluation forms will be collected twice (after 6 weeks of outpatient therapy and at end of outpatient therapy). By looking at the progression (or regression) of these scores, we will also be able to determine if ease of use of the technology increased with the accumulation of training sessions (or not).

All the data will be entered to the central data management system remotely.

o **Data Storage and Confidentiality.** Each subject will have his/her name encoded such that the experimental and clinical measures will not log the participant's real name. The only mapping between the assigned encoded ID and the participant's real identity will be on the consent forms. These will be kept under lock by:

1) Tapia OT and Dr. Kim for the participants early post-stroke PowerBack Rehabilitation;
2) Dr. Barrett for the participants early post-stroke training at Kessler Foundation

The computerized data will be uploaded on a cloud secure database. Access to the database will only be granted to the research team, and will be password protected. Paper records involving the motor and cognitive evaluations as well as the subjective evaluation questionnaires will also be kept locked by Tapia OT, Dr. Kim, Dr. Hundal (for the cognitive and emotive evaluations of the feasibility subjects) and AM Barrett MD for the controlled trials subjects at Kessler Foundation.

o **Transition from Research Participation.** Subjects will not have their standard of care or medication interrupted during participation.

iv. **Risk/Benefit Assessment**

o **Risk Category.** Minimal

o **Potential Risk.** Potential risks to healthy subjects participating in usability testing BAC or caregivers for CVA survivors will be minimal. For the subjects early post-stroke there may be some chance of muscle or joint soreness from repeated use of arms and hands during interaction with VR training scenes. However, this will be low, as the games will require everyday movements of the arm and hand. Confidentiality of healthy subject information will be protected via use of number codes for subjects, and no specimens will be taken from the subjects.

Data collected for this investigation will be used to determine the feasibility of the *BAC* virtual reality game rehabilitation system in training the arm/shoulder/hand, as well as cognitive functions. Data will include strength, active range of motion, coordination, motor control, spasticity, arm and hand function, memory and focusing, executive function, and quality of life (depression levels). Risks for all subjects during training include sore muscles from arm/hand training, or neck soreness. We anticipate that the frequency will decrease as participants strengthen their shoulder, arm and hand during training. There is also a risk of increased blood pressure during prolonged exposures to virtual reality games. For all subjects blood pressure and pulse rate will be measured before, mid-session and after each training session.

o **Protection Against Risks.**

Training for subjects at the early post-stroke period will be conducted by trained occupational therapists who are experienced in monitoring exercise levels and handling emergencies. Since subjects are in the sub-acute stage post-stroke additional measures will be taken: a) the session will be shorter; b) difficulty of the games with less demanding position of the upper limb by manipulation of table angle; c) the mandatory mid-session blood

pressure/pulse measures will also serve as rest break; d) blood pressure and pulse rate will be measured at the start. Mid- and end of each session.

In the unlikely event that a subject should require medical treatment, standard emergency medical procedures will be followed. Occupational therapist in the room during training on the BAC system will assist the stroke survivor participants as needed. In case of muscle soreness we will increase rest periods between games for all participants, and reduce difficulty levels as needed. Participants will always exercise in sitting, for increased balance and safety.

Participants will not be allowed to commence, or continue training if their blood pressure/pulse values are determined to be clinically significant by the treating clinicians. In our experience with BrightArm and with BrightBrainer systems, patients tend to relax, and their blood pressure and pulse rate are actually lower at the end of a session. We observed this reduction in blood pressure both in SNF residents chronic post-stroke and in participants with dementia training on BrightBrainer. The BAC arm support has a wireless transmitter to the PC, used to send grasp strength and finger extension data. We will consult with pacemaker manufacturers to make sure such transmission (433 MHz) does not interfere with a participant's device (if there is one). The HTC VIVE tracker used to measure the patient's hand position and orientation uses low-intensity infrared. We do not believe this will pose a health risk to our subjects.

There is also a risk of emotional discomfort if participants are frustrated with the games (either length, or difficulty, or both). For the participants post-stroke we will shorten sessions, and temporarily reduce difficulty levels, until participants feel more comfortable to be challenged. In our 2010, 2011, 2013, 2014, 2018trials participants were happier (less depression) post our experimental therapy. The difficulty of the games will be set automatically based on their prior performance, so as to minimize frustration for not winning. Each participant will have an option to choose the games they want to play.

o **Potential Benefits to the Subjects.** The Centers for Disease Control and Prevention (CDC) has reported that 2009 direct and indirect costs associated with stroke totalled 70 billion. This investigation will develop a new product/system that will improve training techniques for the arm/shoulder/grasp for elderly patients early post-stroke when they have weak arms. The system will provide safe, but intensive training, prone to induce substantially more arm repetitions than conventional care. As such we will better take advantage of a period when the brain has highest plasticity for recovery. The investigation further aims to improve the cognitive/emotive state for stroke survivors.

It is well understood in medical practice, and especially in integrative medicine, that patient morale has a positive effect on health. Our system will keep morale high by enabling participants to win, and by rewarding them through applause, and congratulatory text on the game screen. Participants in the feasibility study will receive about 12 sessions of arm training free of charge. Those in the inpatient and outpatient control study will also receive additional free training time to their customary care. Our prior research has shown improved hand, arm function, memory, focusing, decision making and reduced depression following intensive training in virtual reality.

For individuals with PD this research may uncover knowledge related to the influence of game characteristics on tremor magnitude and frequency. Further knowledge will be gained on potential use of Virtual Reality at treatment modality for this population.

o **Alternatives to Participation.** The sub-acute post-stroke subjects have the alternative to continue with customary rehabilitation without adding the experimental upper body training in virtual reality. The outpatient participants at Kessler Foundation have the alternative to continue their customary outpatient rehabilitation without adding the virtual reality therapy.

The individuals with PD participating in the pilot project at BCI/CCIT site have the alternative of not taking part in the study.

v. **Subject Identification, Recruitment and Consent/Assent**

o **Method of Subject Identification and Recruitment.**

1) Prospective post-stroke subjects will be identified based on their medical records kept at PowerBack Rehabilitation and at Kessler Foundation. Prospective volunteer healthy subjects for the BAC usability will be identified from the list of volunteers kept by BCI at CCIT. Prospective subjects sub-acute post-stroke will be given publicity fliers outlining their studies. Subjects interested to participate will be asked to contact Jonathan Tapia OT at PowerBack Rehabilitation or AM Barrett MD at Kessler Foundation. For subjects admitted for short-term rehabilitation in PowerBack Rehabilitation, Tapia OT reviews their intake medical data and will refer to the PI those that appear to be good candidates for the pilot feasibility study.
2) Prospective inpatient subjects at Kessler Foundation will be referred to AM Barrett MD who will review their intake medical data.

o **Prospective subjects screening** will be done using different scripts at PowerBack (for BAC feasibility) and at Kessler Foundation (for RCT). For example the Kessler script will indicate randomization into an experimental or control group, and inability to guarantee where the prospective subject may be randomized to. The language describing the training will also be different on the two scripts. Those subjects that pass the screening, and wish to participate, will be told to contact Tapia OT (feasibility) or AM Barrett MD (controlled study) for follow up consent process.

Process of Consent. For participants post-stroke the consent process will be administered by Dr. Kim, Tapia OT (at PowerBack) and AM Barrett MD and Nori MD (at Kessler Foundation) prior to their first clinical evaluation pre-therapy. During this process we will explain the experimental system, methods, and the objective of the study, the benefits and potential risks of participation, that the participation is entirely voluntary and free, and that the subject can drop out at any time without repercussions. Each prospective subject will be given 24 hours to make up his/her mind regarding participation. The caregivers of subjects participating in the randomized controlled study will also be consented, so they can provide feedback on recovery and increased ADL independence.

For individuals with PD the consent process will be conducted at BCI by Grampurohit OT PhD

- **Subject Capacity.** We will only include subjects that have the cognitive ability to give consent and who are English speakers. Subjects who do not speak English will not be included in the pool as we will not use translated publicity fliers.
- **Subject/Representative Comprehension.** The consent process will be a dialogue in which patients and their caregivers will be given ample opportunity to ask questions, and be encouraged to participate. Only English-speaking subjects will be admitted in the study, in order to minimize the risk of misunderstandings. The person administering the consent process will make sure that the subjects understand what they will be expected to do during the training, and why, by asking potential subjects to explain to them what they have learned (reverse teaching).
- **Debriefing Procedures.** An exit video interview will be conducted for all subjects training on the BAC. We will follow an established script to insure uniformity.
- **Consent Forms.** Guidelines were followed in the new Consent Form to be used (attached to this application)
- **Documentation of Consent.** Each Consent Form will have a subject ID, and will be in 3 copies. One copy will be given to the enrolled subject (or caregiver), 1 will be held by Dr. Kim and 1 by Tapia OT, Namrata OTor AM Barrett MD, depending on which study component the subject was enrolled in (feasibility or controlled study). These will be hard-copy documents.
- **Costs to the Subject.** Subjects will not incur costs due to participation in this study. Study costs will be paid by the grants received by BCI from NIH and from company internal resources. Parking is free at all clinical locations.
- **Payment for Participation.** Participants in the BAC usability study at BCI/CCIT will receive $25 for each session. At Kessler Foundation all 20 participants in the controlled study will receive $25 for each evaluation session.

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