Official Title: the efficacy of a frequency-tuned electromagnetic field treatment in facilitating the recovery of subacute ischemic stroke patients – a pivotal study (the "EMAGINE" study)

Investigational medical device – BQ 2.0

Unique Protocol Identification Number: BQ5

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Brief Title: EMAGINE – electromagnetic field ischemic stroke – novel subacute treatment

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– STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with: a) the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly; b) the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) E6 (R2); c) the ISO 14155 standard, to the extent of recognition by the local regulations, and, where applicable; d) 21 CFR Parts 11, 50, 54, 56, 812; 45 CFR Parts 46 and 160; European Union (EU) Directive 93/42/EEC and, once applicable, Regulation 2017/745.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) / Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is consented/enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the consent form will be approved by the IRB/EC; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

The Sponsor has taken out an insurance policy for the total duration of the study covering the patients and Investigators with respect to the risks involved in conducting this study according to this protocol.

Sponsor: _____
Print/Type Name:

Signature: _____ Date: _____

– STATEMENT OF INVESTIGATOR

I agree to perform the investigations and to abide by this protocol and assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor or Sponsor's representative and documented approval from the IRB/EC, except where necessary to eliminate an immediate hazard(s) to the study participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments, are appropriately trained, have read the Protocol, Instructions for Use (IFU) and, where required, United States (U.S.) Code of Federal Regulations (CFR) applicable to clinical studies listed above. All personnel involved in the conduct of this study and authorized to perform the study-related tasks/procedures have completed GCP training and, if applicable, Human Subjects Protection Training, and are authorized to perform the study-related tasks/procedures. Although I may have delegated trial-related duties, as the Principal Investigator, I maintain full responsibility for this trial.

Principal Investigator: _____
Print/Type Name:

Signature: _____ Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The efficacy of a frequency-tuned electromagnetic field treatment in facilitating the recovery of subacute ischemic stroke patients – a pivotal study (the "EMAGINE" study)
Unique Protocol Identification Number	BQ5
Study Design	Prospective, multicenter, double-blind, randomized, sham-controlled, parallel two-arm study, following a sample-size–adaptive design with a single planned interim analysis.
Study Phase	Pivotal
Sponsor Representative	**Israel**: Assaf Lifshitz, VP of Operations, 3.7 Hi-Tech Village, Edmund J. Safra Campus, Hebrew University, Jerusalem, Israel; Phone +972 (54) 4586787; E-mail: assaf@brainqtech.com
Investigational Device Name	BQ 2.0
Investigational Device Description and Regulatory Classification	BQ 2.0 is a wearable medical device that produces and delivers non-invasive, extremely-low–intensity and low-frequency, frequency-tuned electromagnetic fields in order to stimulate neuronal networks with the aim of reducing disability and promoting neurorecovery. The technology behind the therapy utilized explanatory machine learning and Brain-Computer Interface tools to identify high-resolution spectral patterns that characterize motor functions; the tools are based on a large database of electroencephalography (EEG) spectra taken during functional motor tasks. These spectral patterns are then translated into a non-invasive electromagnetic field treatment, which applies similar patterns directly to the patient's central nervous system (CNS).
Investigational Device Use in the Study:	In this study, BQ 2.0 is intended to reduce disability in adult patients with subacute ischemic stroke, with a moderate to severe disability which includes an upper extremity motor impairment. BQ 2.0 will be used for 9 weeks in conjunction with physical and occupational therapy (PT/OT) and under periodic supervision (either remote or in-person) of a

	trained site study team member. Treatments may be administered in multiple settings [eg, acute care hospital (ACH), inpatient rehabilitation facilities (IRF), Skilled Nursing Facility (SNF), home or other outpatient setup].
Study Population:	The study will enroll up to 150 adult patients with subacute ischemic stroke, with a moderate to severe disability which includes an upper extremity motor impairment, who will be assigned (1:1 allocation ratio) to either active or sham study intervention using BQ 2.0, initiated 4-21 days after the index stroke event. Following the interim analysis, the sample size may be increased up to 344 subjects. Total enrollment from each site to be no more than 20% of the total sample size.
Study Description:	The study intervention will be initiated 4-21 days after the index stroke event and will consist of a total of 45 sessions over a period of 9 weeks (5 treatments per week). Each session will last 60 minutes during which 40 consecutive minutes of active or sham study intervention using BQ 2.0 will be administered. Each study group will be guided by the BQ 2.0 application and asked to perform a standardized, pre-defined and evidence-based physical and occupational therapy regimen concurrent with the study intervention. The PT/OT regimen applied in both treatment and sham controlled groups is aligned with the Class 1 level A recommendation for patients with stroke to participate in a home-based rehabilitation program.[1] BQ 2.0 does not produce any noticeable sound, light or sensation in connection with the stimulation which may disclose the arm assignment, making it ideal for testing in a sham-controlled setup. During sham treatment sessions, for purposes of maintaining the blind, the device will function as if it is delivering the therapy (i.e., the device will turn on and all indicators will function), but the frequency and intensity parameters that are not visible to the subject or site study members will be set to zero so that no stimulation is delivered. **Screening phase** Prospective subjects, who are 3 to 21 days post-stroke, will be consented to participate in the study at either: a) a participating ACH, prior to anticipated transfer to a participating IRF, SNF, outpatient, or home setting; or b) at a participating IRF, SNF, outpatient, or home setting.

[1] Winstein CJ, Stein J, Arena R, et al. Guidelines for Adult Stroke Rehabilitation and Recovery. *Stroke* 2016; 47: e98–e169.

	Consented subjects, who are 4 to 21 days post-stroke will be screened for eligibility to participate in the treatment phase of the study. Efforts should be made to complete enrolment, randomization and initiate treatments as early as possible within the window of recruitment, and target to complete a first treatment within 4 weekdays from admission to the participating site. **Treatment Phase** Eligible subjects will be randomly assigned, at a 1:1 allocation ratio, to either the active or sham study intervention groups. Randomized patients will receive active or sham study intervention sessions using BQ 2.0 (active or sham therapy, respectively), starting 4-21 days after stroke onset and no later than 2 days after randomization. Sessions will be conducted 5 times a week. Each session will last ~60 minutes, with active or sham field being turned on for up to 40 minutes. The only difference between the BQ 2.0 active stimulation and sham therapy is that the sham device does not generate electromagnetic fields during treatment. Subjects in both the active intervention group (BQ 2.0 group) and sham group will be asked to perform device guided physical and occupational therapy activities during each session. Participation in the study will not replace any of the usual care patient should receive. During the study, 45 sessions of active or sham therapy will be conducted in either inpatient, outpatient or home setting. A trained member of the site study team (the "**Clinic Operator**") will be responsible for training and approving the subject's caregiver to operate the session independently. Before an approval to operate a session independently (the "**Approval**") is granted by the Clinic Operator, a Clinic Operator will train the caregiver and supervise the sessions, either in-person or remotely. Once an Approval was granted, sessions will be conducted with the assistance of a caregiver while the Clinic Operator will provide periodic oversight (combined audio and video remote conferencing or audio only, if video is not available). If needed, and at their discretion, the Clinic Operator may join sessions following the Approval too. Any adverse events and device deficiencies occurring during the period of subject's participation will be recorded.

	Subjects will undergo a detailed interim outcome assessment on the 20th (±4) day of treatment, and a detailed primary endpoint outcome assessment on the 90th (±15) day after the onset of the index stroke. In addition, a focused, long-term outcome assessment on the 180th (±15) day after the onset of the index stroke will be performed.
Objectives:	**Primary Efficacy** To show that the BQ therapy is effective in reducing global disability at 3 months post-stroke in disabled patients with upper limb motor impairment when initiated 4 to 21 days following an ischemic stroke. **Secondary Efficacy** To show that the BQ therapy is effective in reducing upper and lower limb impairment, and improving upper limb functionality, health-related quality of life (HRQoL), and level of participation in instrumental activities of daily living (ADL) at 3 months post-stroke, when initiated 4 to 21 days following an ischemic stroke. **Safety** 1. To characterize the safety profile of the BQ therapy. 2. To show that the BQ 2.0 performs reliably **Tertiary/Exploratory** 1. To show that the BQ therapy is effective in reducing cognitive impairment, depression and fine-grained level of disability at 3 months post-stroke, when initiated 4 to 21 days following an ischemic stroke. 2. To characterize the long-term effect at 6 months post-stroke of the BQ therapy effect on upper limb functionality and health-related quality of life (HRQoL). 3. To formally evaluate the cost-effectiveness of the BQ therapy over a lifetime horizon from the perspective of the United States healthcare system. 4. To explore the relationship between adherence to treatment as measured by the Qompass and clinical outcomes
Endpoints:	**Primary efficacy endpoint** Modified Rankin Scale (mRS; global disability) change from baseline (4-21 days post-stroke) to 90 days post-stroke. **Secondary efficacy endpoints**

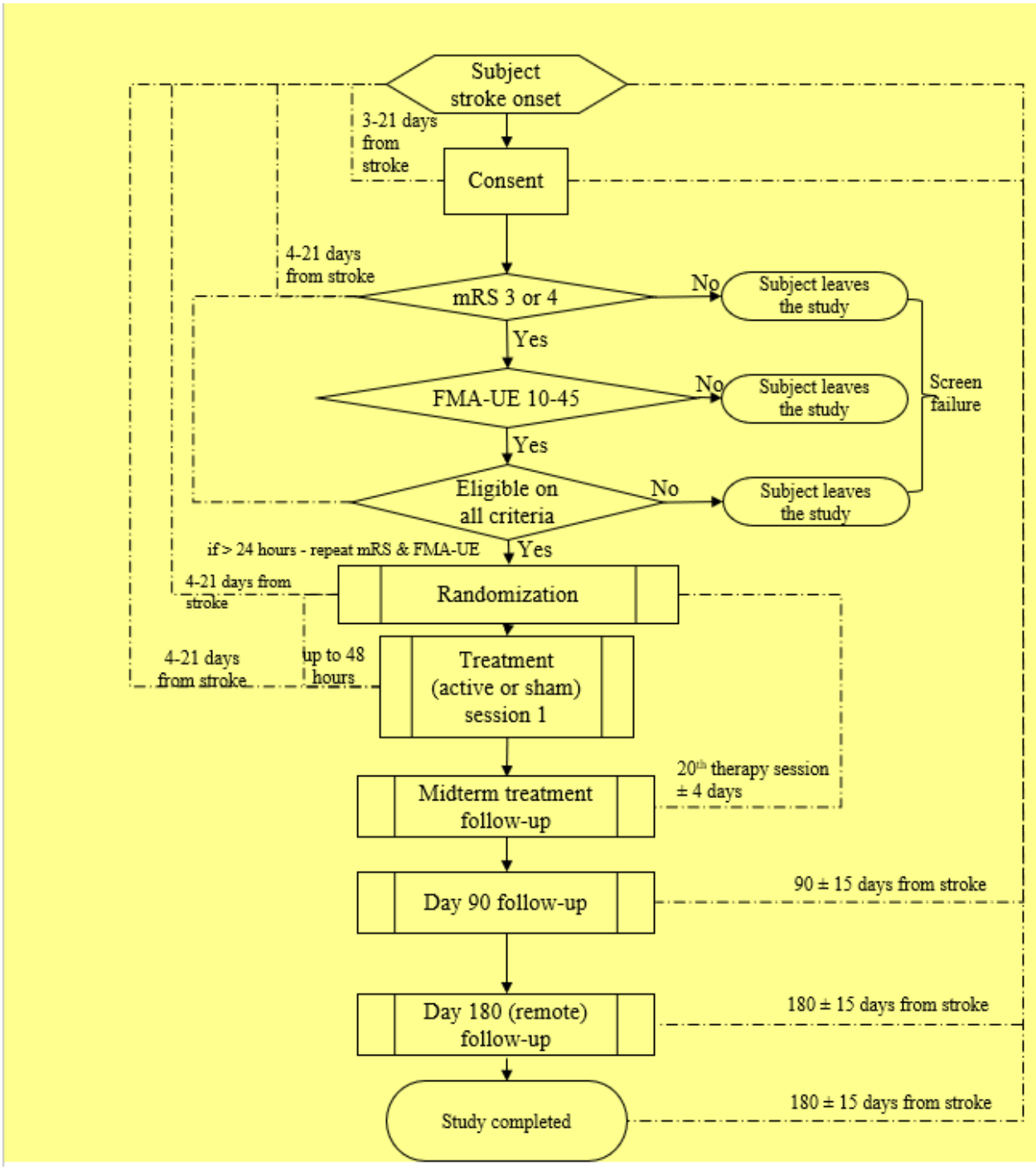
	The secondary efficacy endpoints will be analyzed in stepwise gatekeeper manner to control for multiplicity. The hierarchical order of analysis will be: 1. Lead secondary endpoint: Fugl-Meyer Assessment for Upper Extremity (FMA-UE; upper limb function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke 2. Box and Block Test (arm motor function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 3. 10-meter Walk Test (gait speed) – change from baseline (4-21 days post-stroke) to 90 days post-stroke 4. Stroke Impact Scale Hand Domain (patient-reported hand function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 5. Stroke Impact Scale 16 (patient-reported physical functional limitation) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 6. 5-level EQ-5D (health-related quality of life) at 90 days post-stroke. **Safety** 1. Serious procedure– or device–related adverse events. 2. Device deficiencies to detect operational reliability. **Tertiary/Exploratory** 1. Montreal Cognitive Assessment (global cognitive function) – at 90 days post-stroke. 2. Patient Health Questionnaire-8 (depression) – at 90 days post-stroke. 3. Academic Medical Center Linear Disability Scale (granular level of disability) at 90 days post-stroke. 4. Modified Rankin Scale (global disability) change from baseline (4-21 days post-stroke) to 180 days post-stroke. 5. Stroke Impact Scale Hand Domain (patient-reported hand function) – change from baseline (4-21 days post-stroke) to 180 days post-stroke. 6. 5-level EQ-5D (health-related quality of life) at 180 days post-stroke. 7. Formal cost-effectiveness analysis over a lifetime horizon from the perspective of the United States healthcare system. 8. Relationship between adherence to treatment as measured by the Qompass and the clinical outcomes
Eligibility Criteria	**Inclusion criteria**: 1. mRS score of 3 or 4. 2. FMA-UE score between 10-45 (inclusive) of impaired limb. 3. Age 22 to 85 years of age (inclusive).

	4. Diagnosed with an ischemic stroke, confirmed by CT[2] or MRI[3] imaging. 5. Four to 21 days from stroke onset (or last known well). 6. Pre-stroke mRS of 0 or 1. 7. Able to sit with the investigational device for 40 consecutive minutes, in the opinion of the investigator or designee. 8. Can follow a 3-step command, such as "take the paper, fold it in half, and return it to me". 9. Willingness to participate in occupational/physical therapy activities during study intervention sessions. 10. Availability of a relative or other caregiver able to assist during PT/OT treatment, and to operate an application installed on a mobile device, including a video call. 11. If female, not pregnant (as confirmed by a urine or a blood test, or as determined by an official medical document) or breastfeeding and with no ability to become pregnant or on an acceptable method of contraception during the study. 12. Informed consent signed by subject (if competent) or legally authorized representative. **Exclusion criteria**: 1. Severe neglect impairment (NIHSS[4] item 11, score = 2) or neglect that is severe enough to interfere with reasonable performance of study procedures. 2. Implanted active electronic or passive MR-incompatible devices. 3. Previous ischemic or hemorrhagic stroke within 2 weeks before the index stroke. 4. Pre-existing neurological condition (eg, Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury, spinal cord injury) or physical limitation that would interfere significantly with the subject's participation in the study and/or confound neurological or functional evaluation. 5. Active epilepsy or currently taking anti-epileptic medication (indicated for the treatment of a seizure disorder), or seizure in the last 5 years. 6. Significant visual disturbances that cannot be corrected and that would interfere significantly with the subject's participation in the study and/or confound neurological or functional evaluation. 7. Unstable serious illness/condition (eg; active cancer, severe heart failure, active psychiatric condition) or life expectancy of less than 12 months.

[2] Computed tomography
[3] Magnetic resonance imaging
[4] National Institutes of Health Stroke Scale

	8. A known severe allergic reaction to acrylic-based adhesives. 9. Ongoing alcohol abuse and/or illicit drug use. 10. Participation in another trial that would conflict with the current study or clinical endpoint interference may occur. 11. Employee of the Sponsor. 12. Prisoner.
Description of Sites/Facilities Enrolling Participants:	This is a multicenter study that will be conducted at approximately 20 centers.
Study Duration:	Estimated time to complete enrollment: 24 months Estimated time from study initiation until completion of data analyses: 33 months.
Participant Duration:	From 3-21 days post stroke until 180 (±15) days post-stroke.
Statistical Considerations	Full details of the statistical analysis plan are presented in the statistical section of the protocol, including definition of analysis sets, alpha level handling and adjustments for multiplicity, poolability, etc. **Statistical hypothesis** Null hypothesis: Mean change in mRS score from baseline (post-stroke day 4-21) to 90 days post-stroke in the BQ 2.0 group = mean change in the sham group. Alternative hypothesis: Mean change in mRS score from baseline (post-stroke day 4-21) to 90 days post-stroke in the BQ 2.0 group ≠ mean change in the sham group. **Interim analysis** One interim analysis is planned after 61% evaluable participants have completed the 90-day visit with rules for sample size reassessment or stopping for futility.

1.2 SCHEMA


Subject stroke onset
3-21 days from stroke
Consent
4-21 days from stroke
mRS 3 or 4
No
Subject leaves the study
Yes
FMA-UE 10-45
No
Subject leaves the study
Screen failure
Yes
Eligible on all criteria
No
Subject leaves the study
if > 24 hours - repeat mRS & FMA-UE
Yes
4-21 days from stroke
Randomization
4-21 days from stroke
up to 48 hours
Treatment (active or sham) session 1
Midterm treatment follow-up
20th therapy session ± 4 days
Day 90 follow-up
90 ± 15 days from stroke
Day 180 (remote) follow-up
180 ± 15 days from stroke
Study completed
180 ± 15 days from stroke

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Pre-Screening Phase**	**Screening, Enrollment & Baseline Visit**	**Treatments 1-20**	**Midterm follow-up (in clinic[5])** ± 4 days from 20th treatment)	**Treatments 21-45[6]**	**90 Day Primary outcome assessment (in clinic[7])** 90 Day ± 15 days post-stroke	**Additional follow-up (remote)** 180 Day ± 15 days post-stroke
Informed consent		X					
modified Rankin Scale (mRS)		X[8]		X		X	X
Inclusion/exclusion criteria review	X[9]	X[10]					
Randomization		X					
Investigational/sham device use and intra-session PT/OT			X		X		
Fugl-Meyer Assessment for Upper Extremity (FMA-UE)		X		X		X	
Box and Block Test (BBT)		X		X		X	
Stroke Impact Scale (SIS) Hand Domain		X		X		X	X
Stroke Impact Scale 16 (SIS-16)		X		X		X	
10 Meter Walk Test (10MWT)		X				X	
Shoulder Abduction and Finger Extension (SAFE) score		X					
5-level EQ-5D (EQ-5D-5L)						X	X
Montreal Cognitive Assessment test (MoCA)						X	

5 In special circumstances and subject to the approval of the Principal Investigator, visit can be conducted in an outpatient setting or via combined audio and video remote conferencing or audio only, if video is not available.

6 Missed or incomplete treatment sessions can be completed up until the day before the 90 Day follow up visit (day 90 ±15).

7 In special circumstances and subject to the approval of the Principial Investigator, visit can be conducted in an outpatient setting or via combined audio and video remote conferencing or audio only, if video is not available.

8 To be performed after consenting and before all other screening activities.

9 Brief review to determine initial eligibility for and interest in the study

10 mRS and FMA-UE are to be performed again before randomization if more than 24 hours have elapsed since the assessment of the mRS and FMA-UE. If assessments are performed again and subject is eligible, the later scores will serve as the baseline scores and for stratification.

Patient Health Questionnaire-8 (PHQ-8)						X	
Academic Medical Center Linear Disability Scale (ALDS)						X	
Health economics data capture				X		X	X
Demographics		X					
Medical history		X					
Concomitant medications review and evaluation		X	X	X	X	X	X
Vital signs		X		X		X	
Pregnancy test[11]		X					
Adverse events review and evaluation		X	X	X	X	X	X
PT/OT done outside of study review			X	X	X	X	
Investigational/sham device use			X		X		
Blinding effectiveness assessment						X	
Device deficiencies review and evaluation			X	X	X	X	
National Institutes of Health Stroke Scale (NIHSS) score		X					
Transcription of last mRS score given as part of routine care prior to discharge from ACH		X[12]					
Transcription of blood count[13]		X					
Provision of imaging data[14][15]		X					
Complete case report forms		X	X	X	X	X	X

[11] In women of childbearing potential, a urine or a blood test, or based on official medical documentation.

[12] To be retrieved after consenting; this score will not serve as the baseline mRS score.

[13] Limited to transcription of red blood cell distribution width and absolute white cell count values from the blood count performed at the time of admission into the Intensive Care Unit (ICU) or ACH (the earlier available of the two).

[14] Provision of Digital Imaging and Communications in Medicine (DICOM) files obtained from all computed tomography (CT), CT angiography (CTA), CT perfusion (CTP), and brain magnetic resonance imaging (MRI) perfusion/diffusion-weighted imaging (DWI/PWI) / fluid attenuated inversion recovery brain magnetic resonance angiography (FLAIR), and brain magnetic resonance angiography (MRA) studies available from the first 7 days in the ACH.

[15] If multiple images are available from different days/recording sessions at the acute stay, collect the first image (must) and the last image. MRI images are preferred over CT

2 INTRODUCTION

2.1 STUDY RATIONALE

Stroke is a leading cause of major adult disability in the United States. The preponderance of strokes in the US (80%-87%) are ischemic, with a smaller proportion hemorrhagic (1, 2). Effective interventions exist for ischemic stroke in the acute phase. These include recanalization therapies, such as intravenous thrombolysis (IVT) with alteplase (3-12) and mechanical endovascular thrombectomy (EVT; (13, 14)). However, these therapies are available to only a relatively small subset of patients (5%-15%) and within a relatively short post-event–onset window (15). Moreover, even among patients treated with combined IVT and EVT, 73% have a disabled or fatal outcome at three months (16).

Beyond acute care, stroke rehabilitation is the focus, a combined and coordinated use of medical, social, educational, and vocational measures to retrain individuals who have suffered strokes that resulted in life-limiting disability. Hemiparesis (weakness or inability to move on one side) and upper limb motor impairment are some of the most common disabling symptoms of stroke (17). As many as 88% of patients with acute stroke have hemiparesis (18). Ample evidence supports the premise that early initiation of physical therapy favorably influences motor recovery from stroke (19). It is recognized that highly intensive and highly repetitive physical therapeutic programs probably provide direct influence on the process of functional reorganization in the brain and enhance neurologic recovery (20). A key aspect of neuroplasticity that has important implications for rehabilitation is the fact that the modifications in neuronal networks are use-dependent. Animal experimental studies and clinical trials in humans have shown that forced-use and functional training contribute to improved function, emphasizing the benefit of intense physical therapy regimens as a treatment of stroke symptoms (21). Additionally, experimental evidence indicates that plasticity can be altered by external factors, including pharmacologic agents, electrical stimulation, and environmental stimulation (22).

Nonetheless, despite receiving current standard of care rehabilitation therapy, a large proportion of stroke patients finish their rehabilitation therapy course with residual and substantial deficits, including in the upper limb.

Consequently, although there are demonstrated benefits of select acute ischemic stroke therapies and rehabilitation programs, many stroke patients are left with persisting, lifelong impairments.

This trial tests a promising new intervention to promote post-stroke neural reorganization and functional recovery. Multiple studies have shown that exposing impaired neuronal networks to oscillating fields that are similar to those experienced in a healthy central nervous system, promotes network reorganization post-injury. The cardinal frequencies of these oscillations have

been identified using electroencephalographic recordings of healthy and impaired populations. The BQ 2.0 device transmits these frequencies via non-invasive, extremely-low–intensity, low-frequency electromagnetic field exposure (BQ therapy). These frequency-tuned exposures are within the same frequency and intensity ranges as those fields generated about the neurons in an active network. As network dynamics have been shown to be sensitive to endogenous (23, 24) and external electric and magnetic fields at specific frequencies (24-26), this treatment is designed to support the return of synchronization within the targeted networks and, ultimately, network reorganization.

The BQ 2.0 device is intended to be used adjunctively with the current standard of care. During the exposure to the device generated electromagnetic fields (BQ therapy), patients perform device-guided physical and occupational exercises to further support their recovery process and drive neural reorganization. The exercises patients are asked to perform during BQ therapy are evidence-based PT and OT regimens focused on upper extremity rehabilitation.

Initial clinical studies suggest that the BQ therapy started subacutely after ischemic stroke may decrease the degree of disability in stroke patients. The study to be conducted under this protocol is designed to confirm the initial findings and provide evidence of efficacy and safety of the BQ 2.0 in treatment of ischemic stroke patients.

2.2 BACKGROUND

Ischemic stroke is injury to the brain due to vessel occlusion, depriving a brain region of blood flow carrying oxygen and nutrients (27). Ischemic stroke accounts for the great preponderance (80%-87%) of all stroke in the United States, with hemorrhagic stroke, injury to the brain due to vessel rupture, causing the remainder (1, 2). Etiologically, ischemic stroke is caused most often by embolism from the heart, artery-to-artery embolism, and in-situ small vessel disease. In one-fifth of cases, the cause is cryptogenic (28).

Ischemic stroke is a leading cause of long-term disability and patient mortality worldwide (29). Overall, stroke accounts for almost 5% of all disability-adjusted life-years (30) and 10% of all deaths worldwide (31). In the United States, over 795 000 strokes occur each year (2), of which approximately 610 000 are first attacks, and 185 000 are recurrent strokes. Stroke claims more than 150 000 lives annually but leaves even more patients alive but disabled. About 7 million post-stroke survivors live in the United States (32) and about 2.5% of its population report disability due to stroke. The impact of stroke to the United States economy, including the cost of health care services, medicines to treat stroke, and missed days of work, is over $45 billion (33, 34) and is forecasted to grow substantially, in parallel to the expected increase of 20% in ischemic stroke incidence by 2030 (33).

The leading effective interventions for ischemic stroke in the acute phase (first 0-24h) are reperfusion treatments – IVT with alteplase (3-12) and EVT (13, 14). However, these therapies are available to only a relatively small subset of patients (5%-15%) and within a relatively short post-event–onset window (15). Moreover, though of proven benefit, these treatments are far from a panacea. Even among patients treated with combined IVT and EVT, 73% have a disabled or fatal outcome at three months (16).

Importantly, the effect of acute ischemic stroke treatments upon final 3-month disability outcome is determined by early clinical and imaging outcomes at 24-96 hours. At least 8 multicenter trials and registries studies, enrolling a collective total of 10 494 acute ischemic stroke patients treated with supportive care, IV thrombolysis, and/or endovascular thrombectomy have found that the dominant independent early predictors of 3-month disability outcome are patient age, extent of neurologic deficits at 24-48 hours on the NIHSS, and infarct extent at 24-48 hours (35-42). Reperfusion therapy has no independent influence on the trajectory of patient recovery, in terms of disability, from 48 hours to day 90 (35).

The initial evaluation and management of ischemic stroke patients in ACHs typically lasts between 2-9 days (median 4-5 days). Ischemic stroke patients are then discharged to one among a range of continued care settings, including their own homes, IRFs), and skilled nursing facilities (SNFs; (43)). The standard of care for ischemic patients in the subacute and chronic stages has two main elements. The first is medical and surgical therapies to prevent recurrent stroke, including administering anti-thrombotic agents and controlling key modifiable risk factors. The second is rehabilitation therapy to maximize recovery from the index stroke. Rehabilitation therapies are functional and impairment-specific, focusing on the areas of loss which are individual to each patient (44).

In the case of motor impairment, one of the most common and devastating deficits after stroke, extensive OT and PT regimens are regularly implemented, focusing on individual areas of gross and fine motor impairment. PT/OT typically involves a variety of specific motor skill exercises, mobility training, range of motion therapy and constraint-induced mobility therapy (CIMT). The recommendation is that physical rehabilitation be initiated as early as is tolerated after the first 24 hours from stroke onset (19). The intensity of therapy depends on patient ability as well as treatment setting. There is strong evidence for benefit from PT/OT interventions involving highly intensive and highly repetitive task-oriented and task-specific training (20). CIMT has been found to be moderately effective and recommended as part of PT/OT regimens for appropriate patients (45).

Direct motoric and cognitive interaction with a physical and occupational therapist remains the mainstay of rehabilitation therapy for residual motor impairment in the United States. Among ischemic stroke patients with a moderate to severe disability at the end of the acute care hospital

phase, multiple studies have demonstrated the typical subsequent course is some improvement in deficits over the next 3 months followed by stabilization at a permanent level of functioning. Multiple studies have shown that, with standard rehabilitative care, moderately-severely disabled patients improve by a mean of around 1.1 points on the mRS scale by day 90 (46-48). Taking into account this improvement, the mRS level at the conclusion of acute care, upon stabilization from acute injury is strongly and consistently correlated with mRS at day 90 (49). This improvement is consistent across broad patient groups, regardless of age, sex, and ischemic stroke mechanism. However, this improvement is typically incomplete, and most patients are then left with residual, permanent disability.

Some technologies have been tested, generally in small trials, for potential to further improve recovery above this standard of care, including neuromuscular electrical stimulation (NMES), functional electrical stimulation (FES), and robot-assisted therapy (50, 51). Although of some promise, none of these devices has been yet demonstrated to be unequivocally beneficial and none are deemed to be elements in the current standard of care in the United States (43).

In sum, although there are demonstrated benefits of select acute ischemic stroke therapies and PT/OT rehabilitation programs for stroke, a substantial majority of stroke patients, roughly 90% (2), are left with persisting, lifelong impairments despite receiving the current standard of care. Thus, while the standard of care may be effective and allow for a meaningful reduction in disability, for those patients with a moderate to severe disability, these changes are often insufficient. In these patients, a chronic disability persists, not allowing them to return to work or participate in their usual pre-stroke activities.

Potential role of the investigational device

In the subacute phase after ischemic stroke, the central nervous system (CNS) attempts to repair and reorganize itself by reorganizing damaged networks and forging new connections to restore motor and cognitive functions (52-54). Following injury, and before such reorganization takes place, neuronal network connectivity is disturbed, which is reflected in perturbed oscillatory patterns on electroencephalography (EEG; (53, 55, 56)).

The mechanism of action proposed by BrainQ Technologies Ltd. is that exposing impaired neuronal networks to oscillating fields that are similar to those experienced in a healthy CNS, promotes network reorganization post-injury. The cardinal frequencies of these oscillations are identified using EEG recordings of healthy and impaired populations, and transmitted via non-invasive, extremely-low–intensity, low-frequency electromagnetic field exposure (Electromagnetic Network Targeting Field or ENTF; BQ therapy). These frequency-tuned exposures are within the same frequency and intensity ranges as those fields generated about the neurons in an active network. As network dynamics have been shown to be sensitive to

endogenous (23, 24) and external electric and magnetic fields at specific frequencies (24-26), this treatment is designed to support the return of synchronization within the targeted networks and, ultimately, network reorganization.

In order to identify oscillatory patterns in the healthy CNS, most relevant to our treatment, BQ 2.0 utilizes explanatory (supervised) machine learning (ML) tools on labeled EEG data, recorded during specific motor paradigms.

Supervised learning is a ML technique, which uses labeled data, in which the correct output (label) is given to the algorithm in conjunction with every input sample (57). The goal of this technique is to determine a function or model, referred to as the classifier or the regressor, that can predict the correct output for every input in a novel dataset.

Supervised learning is used as a tool to analyze EEG recordings, primarily for diagnostic purposes of neurological conditions such as epilepsy (58-60). This method requires the design of a paradigm to allow for the collection of labeled EEG data. In such cases, the goal of the classification algorithm is to predict the patient's condition with maximum accuracy. The features that contribute to the classification are usually of limited interest and are often not readily interpretable.

In contrast, when explanatory ML tools are used, the focus is analyzing the features that are most informative to the classification. This approach may reveal biological insights (61).

Taken together, BrainQ Technologies Ltd. used explanatory ML to extract spectral features/patterns to inform the frequency selection of the BQ therapy. To identify these features, BrainQ Technologies Ltd. collected large quantities of labeled EEG data from both healthy and impaired individuals while performing specific motor tasks. The data underwent preprocessing, subsequently, a supervised learning classifier was trained to achieve high classification accuracy between different states (ie, hand grip vs. rest) and identified specific features critical to each state. BrainQ Technologies Ltd. then incorporated prior knowledge to selectively identify a subset of the extracted features most relevant to neurological recovery to inform the BQ therapy frequencies. The frequency identification analysis has already been completed for this version of the device and it is static.

2.2.1 SUMMARY OF FINDINGS FROM NONCLINICAL STUDIES OF THE BQ 2.0

The pre-clinical studies performed with the BQ 2.0 are shortly tabulated below (Table 1). For a detailed summary, please refer to the study investigator's brochure (IB).

Table 1. Short summary of pre-clinical evaluation of the BQ 2.0

Test Name	Objectives and Endpoints	Verification Methods	Sample Size	Main Results
BRQ-001-EF The Influence of Electromagnetic Exposure on Neurogenesis in Mice	**Objectives**: To assess the efficacy of extremely low frequency (ELF) magnetic fields exposure on neurogenesis in adult mice. **Endpoints**: Body weight (1/week), clinical signs, morbidity and mortality (2x/day), Social recognition, gross pathology), histological analysis. When possible, scores were analyzed by two-way ANOVA with Bonferroni correction ($p \leq 0.05$)	Randomized, sham-controlled. Ten groups of 6 mice were exposed to 0, 2, 4, 6, or 8 minutes of a 10 Hz field either daily or every other day for 27 days and sacrificed for necropsy at day 54. An additional 4 groups of 4 mice at 0 and 8 min, daily and every other day, were treated for the same 27 days, but sacrificed at day 114 for necropsy.	76 C57BL/6 male mice	Histological evidence of increased proliferation as well as differentiation and cell survival under certain exposure conditions. Treatment parameters of group 4M (2 min of exposure every other day) produced the optimal increase in oligodendrocyte proliferation and survival. These findings indicate the presence and activity of plasticity processes following electromagnetic field (EMF) exposure. No pathological findings were identified in the brain structures.
BRQ-002-EF The Influence of Electromagnetic Exposure on Neurogenesis in Mice Following Traumatic Brain Injury	**Objectives**: To assess the efficacy of ELF magnetic fields exposure in adult neurogenesis in mice after traumatic brain injury. **Endpoints**: Body weight (daily for first week, every other day for second week, weekly thereafter), Neurological severity score (NSS), morbidity and mortality (2x/day), histological analysis. When possible, scores were analyzed by two-way ANOVA with Bonferroni correction ($p \leq 0.05$)	Randomized, sham-controlled. Mice were divided into 7 groups, including a control group. The groups varied in frequency exposure and duration of exposure (2 min. or 8 min.). Two frequencies (7.86 Hz. And 10 Hz.) and two timetables (once a day and once every other day) were evaluated. Animals in some subgroups were sacrificed at the end of the study, while others were subjected to continued observation.	50 male C57BL/6 mice	No adverse events or abnormal changes in body weight were recorded in any study animals. Results indicate an effect of both the exposure frequency and exposure schedule in improving motor recovery in treated mice following TBI. Mice with daily exposure at 7.86 Hz showed the greatest behavioral recovery. Additionally, no significant results were reported for the animals subjected to continued evaluation.
BRQ-003-EF The Influence of Electromagnetic Exposure on Neurogenesis in Rat Stroke Model	**Objectives**: To assess the efficacy of ELF magnetic fields exposure for enhancing neurogenesis in rat after stroke. **Endpoints**: Body weight, NSS, forelimb placement, object recognition, magnetic resonance imaging (MRI), Morbidity and mortality, histological analysis. When possible, scores were analyzed by two-way ANOVA with Bonferroni correction ($p \leq 0.05$)	Randomized, sham-controlled. The 30 animals were divided 5 groups consisting of 6 animals per group, all of which were subject to transient middle cerebral artery occlusion (tMCAO) as a stroke model. EMF exposure was initiated on day 3 post stroke, and was administered for two minutes 3x weekly, at 0 Hz, 3.93 Hz, 7.86 Hz, 15.72 Hz, or 31.44 Hz.	30 male Sprague Dawley rats; transient middle cerebral artery occlusion (tMCAO) stroke model	Consistent (but not significant) trend of higher behavioral scores in treated groups. Results varied with treatment parameters, with the best outcomes in the 3.93 Hz group. MRI results were varied in the small measured sample (one representative from each group). In general, rats showed decreased perilesional edema after treatment as well as lateral ventricle widening. Upon histological analysis no pathological findings were identified. Other results suggested that the electromagnetic effect can induce neural regeneration

				processes following a brain injury.
BRQ-004-EF The Safety of Electromagnetic Exposure in Young and Aged Rats	**Objectives**: evaluating the safety of ELF magnetic fields exposure in young and aged rats. **Primary Endpoints**: Morbidity and mortality, body weight, MRI, gross pathology, and histological analysis. When possible, scores were analyzed by two-way ANOVA with Bonferroni correction ($p \leq 0.05$)	Randomized, sham-controlled. EMF exposures were performed from study day 1, three times a day (morning, noon and afternoon) until study day 14. Animals were exposed to EMF for 20 minutes each time using the same frequency (15.72 Hz.).	22 male Sprague Dawley rats; 11 in each group	No adverse effect of EMF exposure was observed in either young or old animal groups. Higher T2 values indicated improved tissue integrity in brain regions that are normally subject to age-related deterioration. Histological findings identified cell proliferation, indicative of plasticity, but with no distinct differences between groups.
BRQ-005-EF The Influence of Electromagnetic Field Efficacy in Rat Model of Moderate Spinal Cord Injury – Hemi-crush	**Objectives**: To assess the efficacy of ELF magnetic fields exposure on functional loco-motor recovery in adult rats following moderate spinal cord injury (hemi-crush). **Primary Endpoints**: Morbidity and mortality, body weight, clinical signs, Basso, Beattie, and Bresnahan locomotor test (BBB), grid walking test, Flexion reflex, MRI, gross pathology and histological analysis. When possible, scores were analyzed by two-way ANOVA with Bonferroni correction ($p \leq 0.05$)	Randomized, sham-controlled. EMF exposures were performed from study day 1 – 30, for eight minutes a day, five times a week, for the control group (no treatment), and at 15.86 Hz or 26.00 Hz for the treatment groups. From day 31 – 60, EMF exposure was for 20 minutes a day, five days a week, at the specified frequency.	28 male Sprague Dawley rats; T9 hemi-crush	Animal morbidity (including adverse clinical signs) and unscheduled death were observed in all groups and were attributed to the hemi-crush model of spinal cord injury. No adverse events were recorded in animals that completed treatment. There was faster flexion reflex score (sensory function) improvement and more pronounced BBB loco-motor functional score (motor function) improvement in both groups treated with EMF exposure compared to the control group. These effects were faster and more pronounced in the group treated with EMF exposure at 26.00 Hz. Fractional anisotropy (FA) and fiber reconstruction results indicate worsening of condition in control rat, and improvement of condition in treated rat.

2.2.2 SUMMARY OF CLINICAL RESEARCH OF THE BQ 2.0

Clinical investigations have been performed by BrainQ Technologies Ltd., in both stroke and spinal cord injury populations. In stroke patients, a pilot double-blind, parallel-group, randomized sham-controlled trial was performed (BQ3 trial) using the BQ 1.0 device, the direct predecessor of BQ 2.0.

This trial was performed at the BLK Super Specialty Hospital, a multi-specialty hospital located in Delhi, India. The study was supervised by an international contract research organization

(CRO) and conducted in conformance with GCP and in accordance with the principles of the Declaration of Helsinki. Ethics Committee (EC) approval was obtained before the study initiation. All subjects provided written informed consent to participate in the study.

The BQ3 trial enrolled patients diagnosed with a first ischemic stroke, with the diagnosis confirmed by imaging, and patients with a recurrent stroke in whom no previous neurological impairment in the same limb was reported before current stroke. Patients were recruited from 72 hours to 15 days from stroke onset or 21 days from stroke onset, in case the patient was still unstable at day 15. To be considered eligible, patient's FMA-UE had to be in the range of 10-45.

This trial was designed for a population of 50 but was terminated just short of the pre-specified interim analysis (planned at n=26; discontinued at n=25, with EC approval) due to the outbreak of COVID-19.

In total, 28 subjects were recruited to the study, of which 24 were randomized to receive either investigational (n=14) or sham therapy (n=10). Due to randomization error, which was revealed only post data lock and unblinding, two subjects received active treatment instead of sham treatment (n=16 and n=8, respectively). Of the 24 randomized subjects, 21 subjects completed all active (n=13) or sham (n=8) treatments (modified randomized as treated, mRT). To minimize bias, results of the mRT analysis are presented below (Figure 1).

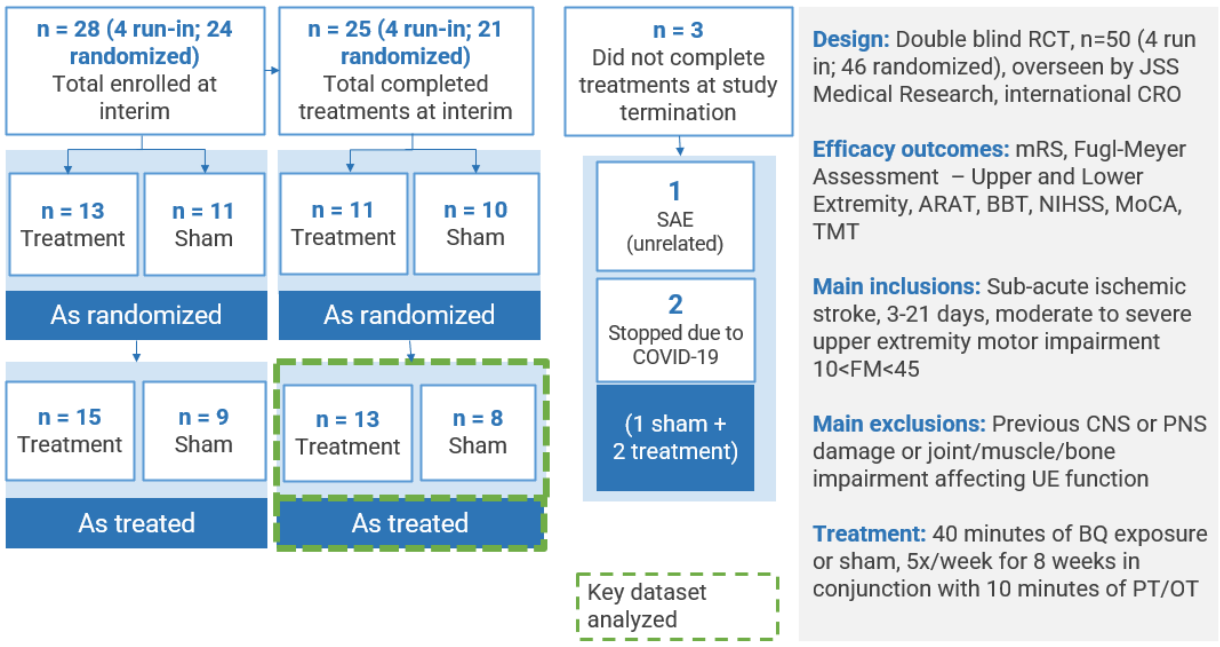


Figure 1. Breakdown of BQ3 trial population, as stipulated and as implemented

In addition to the hospital's standard therapy regimen of 1-hour daily treatments, both study groups sat within the BQ device for the duration of each treatment session and received 10 minutes of upper extremity PT/OT during the treatment session. The only difference between the investigational and sham treatment was whether or not the investigational device generated an EMF. Due to the non-invasive nature of the treatment, as well as the physical characteristic of the EMF, there was no noticeable difference between experimental conditions, and both subjects and operators were truly blinded. No significant differences between the baseline characteristics of the treatment and sham groups were identified.

The first four subjects were considered run-in subjects and were assigned directly to the treatment group. Due to early termination of the study, the expectation for meaningful outcomes beyond mere positive trends was limited. Still, the significant results and positive trends obtained in multiple metrics presented below, establish an indication of the efficacy of the treatment under investigation in reducing global disability in the subacute phase of ischemic stroke.

In a dichotomous analysis, where the percentage of subjects to reach little to no disability (mRS of 0-1) was compared to the percentage of subjects who remain with disability after treatment, the rate of non-disabled outcome (mRS 0-1) at final visit was 77% in the treatment group, versus only 25% of the sham-group subjects ($P = 0.03$). Furthermore, improvement by 2 or more mRS points occurred in 92% of subjects in the treatment group, compared to only 25% of the sham-group subjects ($P = 0.003$). This was reflected in the shift analysis of mRS scores in treated versus control subjects (Figure 2). While the results for the sham group are comparable to other sham data from similar longitudinal studies, the treatment group substantially outperformed investigational devices from other studies, as will be further presented below.

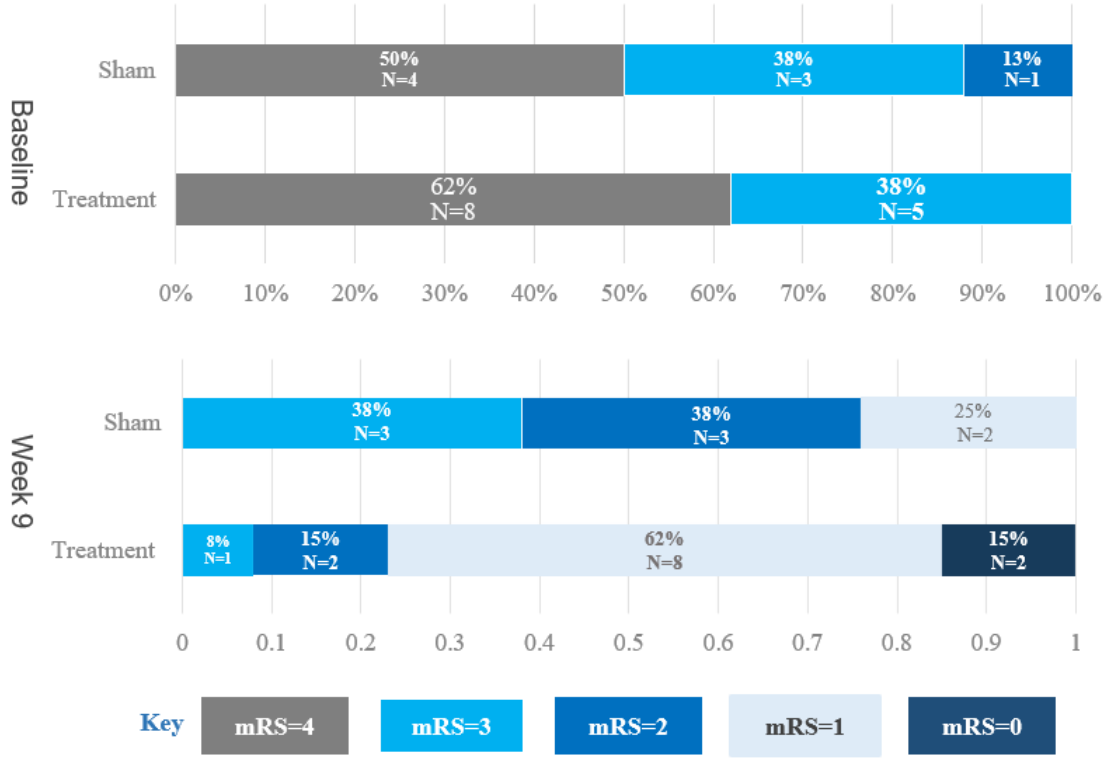


Figure 2. BQ3 study – shift analysis of mRS scores

In an mRS mean change analysis, the subjects in the treatment group experienced a mean change of 2.5 points, compared to 1.3 points in the sham group ($P < 0.001$). When comparing to peer-reviewed publications and published datasets addressing populations comparable to that enrolled in the BQ3 study (baseline mRS of 3-4), the observational (48) and placebo (46, 47) groups perform similarly to BQ3 sham group (Figure 3). By derivation, despite the fact that the BQ3 study enrolled a small number of subjects for statistically-significant conclusions to be drawn, the sham group performed as expected from historical data, while the treatment group substantially outperformed the control groups in the published evidence.

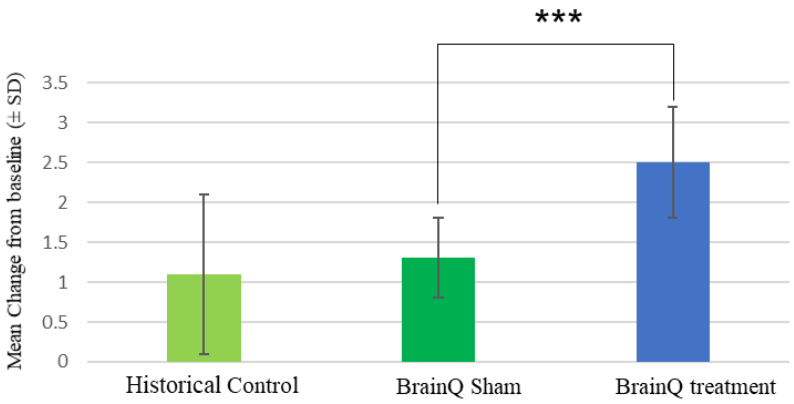


Figure 3. Modified Rankin Scale change in the treatment and control groups of the BQ3 study compared to historical control

An mRS improvement of 2 or more points was observed in 92% of the treatment group subjects, while and improvement of 3 mRS points was found in 54% of the treatment group subjects. Only 25% of the sham group subjects improved by 2 points and a 3-point improvement was not reported in any of the subjects. Individual point shifts can be seen in Figure 4 below.

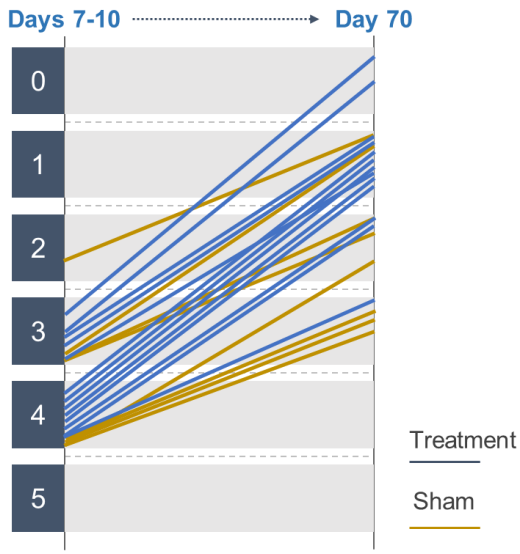


Figure 4. Parallel coordinates plot showing individual changes in mRS from sub-acute phase to 70 days post-stroke in the BQ3 study

To better assess the magnitude of this kind of effect, the mean mRS difference between baseline and post-stroke day 90 mRS obtained with the BQ treatment was compared with its counterpart reported for all the currently recommended acute phase ischemic stroke therapies (Figure 5).

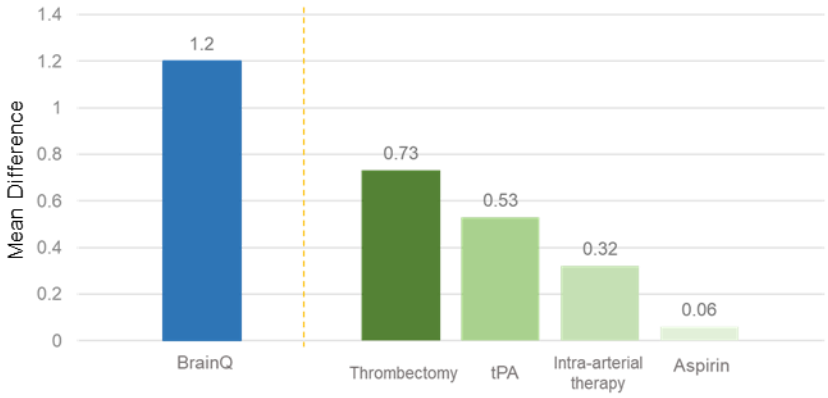


Figure 5. Observed mean difference effect in mRS at 90 days (treatment group – control/placebo group) post-stroke for different acute treatments, compared to the BQ treatment.
The data presented are derived from Saver 2007 (62); thrombectomy data is reproduced from Goyal et al 2016 (16); data on Aspirin is based on a 4-level version of the mRS used in the International Stroke Trial (IST; (63)) and the Chinese Acute Stroke Trial (CAST; (64)), rather than the full 7-level mRS.

Taken together, these findings indicate that the BQ therapy significantly decreases the degree of disability from baseline to final visit. The possibility of a treatment started within the subacute period yielding global improvement in ischemic stroke has the potential for clinically meaningful patient benefit that does not exist with standard of care treatments.

Additional data and significant results from the above trial provide evidence that the reduction in disability achieved by BQ therapy is mediated partially by improvements in motor function, including upper and lower extremity function. In the BQ3 study, BQ therapy demonstrated improvement in several additional measures of motor function, including FMA-UE, FMA-LE, the Action Research Arm Test (ARAT), and BBT (Table 2).

Table 2. BQ3 study – additional results for key endpoints

Endpoint	Timepoint	Difference in mean change*	*P* value
FMA-UE	Week 4	13.6	0.007
FMA-UE	Week 8	8.4	0.06
ARAT	Week 8	9.6	0.087
ARAT-Pinch	Week 8	8.1	0.008
BBT	Week 8	14	<0.0001
FMA-LE	Week 8	3.9	0.03
NIHSS	Week 8	1.8	0.03
* Difference in mean change from baseline between treatment and sham groups			

In terms of safety, there were no device- or procedure-related adverse events (AEs) in this study. The reported AEs included a case of reported headaches and as rehospitalization due to a diagnosis of pancreatic cancer, all deemed unrelated to the device or the procedure.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

To date, there have been no device- or procedure related events in the clinical trials sponsored by BrainQ Technologies Ltd.

The intensity of the BQ 2.0 is in the range of up to 1 Gauss, well below known safety thresholds, and the frequencies used are in the range of those normally observed in the human neural system (65). The device is similar in its field characteristics to pulsed electromagnetic field devices, including commercial home devices. These FDA approved or CE-marked devices use a similar or wider range of intensities and frequencies as the BQ 2.0. Examples of such devices are: Curatron-2000-HT (Curatronic Ltd., Jerusalem, Israel), indicated for treatment of acute and chronic pain as well as rheumatic disorders (mT range [mT = 10 G], frequency 1 –50 Hz), PhysioStim (Orthofix Medical Inc., Lewisville, TX, USA), indicated for treatment of nonunion fractures, and CervicalStim (Orthofix Medical Inc., Lewisville, TX, USA), indicated as an adjunct to cervical fusion surgery in patients at high-risk for non-fusion (1 Hz – 50 KHz, 2-G range), and IMRS (Swiss Bionic Solutions USA Inc., Cooper City, FL, USA), for energy and wellness (mT range, 0.5 –25 Hz). These and similar devices have been used and approved for many years (66-68). Furthermore, the BQ 2.0 intensity is significantly lower than approved stimulation devices, such as transcranial magnetic stimulation which often use fields of 1 – 1.5 T (10 000 – 15 000 G). An example of such a device is BrainsWay (BrainsWay, Jerusalem, Israel), FDA-cleared for a variety of psychiatric indications, and CE-marked for a variety of psychiatric and neurological treatments, including post-stroke rehabilitation.

Potential risks have been identified during risk analysis which included assessment of risks related to the design of the device and evaluation of peer-reviewed clinical evidence on the state of the art in treatments involving or devices utilizing generation of electromagnetic fields.

The following risks may occur during use of the device:

- During the PT session
  - Fatigue during therapy;
  - Pain during therapy;
  - Fractures or abrasions (eg, cuts or bruises) sustained as a result of a fall during lower extremity PT exercises;
- Transient neurological events due to exposure to electromagnetic fields
  - Paresthesia (tickling, numbing sensation in the skin);
  - Phosphenes (seeing light);

- Adverse tissue response or reaction (eg, sensitization, allergy, irritation, inflammation) to the material of a component of BQ 2.0.

The following risks could occur due to guidance-discordant use of the device (ie, misuse[16]), including, but not limited to, in disregard of warnings in the IFU:

- Fractures or abrasions (eg, cuts or bruises) sustained as a result of a fall after attempting to stand up while wearing the BQ 2.0;
- Infection, cross-contamination due to lack of proper disinfection of the device between patients;

The following events may occur due to device malfunction:

- Discomfort or mild pain, headache, paresthesia, nausea and/or dizziness, or seizure due to malfunction of device and excessive electromagnetic emissions;
- Interference with normal operation of active implanted medical device, such as pacemakers, due to malfunction of device and excessive electromagnetic emissions (subjects with implanted active electronic devices are excluded from this study);
- Interference with magnetic-resonance (MR)–incompatible passive implants due to malfunction of device and excessive electromagnetic emissions (at a maximum of 7 G; Subjects with passive MR incompatible devices are excluded from this study).

The following risks could occur due to a cyber-attack:

- Tampering with the device and treatment parameters (eg, treatment intensity, frequency and duration). Tampering with the device could lead to higher intensity emissions. Subjects may experience side effects similar to those caused by stronger electromagnetic fields such as discomfort, headache, increased pain, paresthesia (numbness and tingling) and nausea or harm.
- Tampering with the device may also lead to a lack of intended benefit.
- Privacy breach, patient data or treatment data released.

The following risks have occurred with electromagnetic devices at intensities higher by a factor of approximately 10^4:

- Transient neurological events (rate of occurrence)

[16] per ISO 14971:2019 (definition 3.15): Use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behavior. Readily predictable human behavior includes the behavior of all types of users, eg, lay and professional users. Reasonably foreseeable misuse can be intentional or unintentional.
per ISO/TR 24971:2019: This includes use error (slip, lapse, or mistake), intentional acts of misuse, and intentional use of the medical device for other (medical) applications than intended by the manufacturer

- Mild pain or discomfort/headache (19.7%; (69)).
- Dizziness (2.8%; (69)).
- Seizure (<1%; (70)).
- Nausea (reported in national registries).
- Anxiety, depression, emotional changes, problems with sleep. There was a limited number of reports in national registries for these risks, and importantly to note that majority of the people who experienced these emotional changes had pre-existing psychiatric conditions.
- Transient cognitive changes were rarely reported.
- Twitching was rarely reported.

Burns may occur from overheating of or damage to electrical components in the device.

For the exhaustive list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment, please refer to the IFU.

For risk mitigation activities of the manufacturer, please refer to § 2.3.3.

2.3.2 KNOWN POTENTIAL BENEFITS

In post-acute stroke, improvement is expected to be incomplete using current standard treatment methods. The planned study hopes to provide patients with a safe and effective therapeutic means for the reduction of disability in adult patients with subacute ischemic stroke used in conjunction with physical and occupational therapy.

The BQ 2.0 is designed to offer meaningful clinical benefit as demonstrated in several animal and human studies. The use of BQ 2.0 predecessor devices has provided data showing that the therapy helps restore physical function as well as reduce disability. BQ 2.0 treatment does not interfere with the standard of care a patient receives and can be used in conjunction with pharmacological and physical therapy treatment plans.

In terms of compliance and ease of use, the BQ 2.0 device is non-invasive, patients can be treated in their own wheelchair (when applicable), with no observed pain or discomfort. Treated subjects report that there is no sensation at all associated with the activation of the EMF.

The BQ 2.0 was designed to allow for remote (and specifically home) use from its inception; the need to provide meaningful in-home therapies has been significantly accelerated due to the outbreak of the COVID-19 pandemic. By enabling in home therapy, the Sponsor is able to reduce the risk for patients by way of avoiding clinic visits. The use of the BQ 2.0 is expected to benefit the patient and patient outcomes, with little or no increase in risk based on all clinical experience to date.

Based on the above, it is reasonable to assume that for the BQ 2.0, the expected benefits would outweigh the anticipated risks.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

A risk analysis/assessment for the BQ 2.0 was performed according to ISO 14971. Potential hazards and their risks were reviewed. There are no special design features in BQ 2.0 that pose special safety concerns (eg, presence of medicinal, human, or animal components). Risk analysis focused on six main risk categories:

- Energy, including hazards due to electrical safety, electromagnetic interference, electromagnetic emission, excessive temperature;
- Biological and chemical, including hazards due to cross contamination and biocompatibility;
- Operation, including hazards due to improper functionality of the device, wave generator malfunction, and improper functionality due to user errors;
- Information, including hazards related to insufficient or confusing instructions for use
- Cybersecurity, including potential hazards related to cybersecurity breach such as patient privacy breach, tampering with the application code and/or treatment parameters;
- User errors.

None of the residual risks, following mitigation, were found to be unacceptable and appropriate risk mitigations were implemented.

By design, the BQ 2.0 minimizes safety risks to the subjects as far as possible by lacking sharp corners or edges and protecting the subjects from potentially hazardous contact with electrical components through use of:

- Certified fire-retardant materials insulating relevant electrical components;

As part of the BrainQ Technologies Ltd.'s risk mitigations:

- The maximal field intensity at the applied frequencies is below the threshold for public exposure defined by the International Commission on Non-Ionizing Radiation Protection (71);
- The electronics are limited in the energy that can be produced and, consequently, in the electromagnetic field intensity that can be generated, and are designed to maintain reliable functionality throughout the expected lifetime of the device;

- An internal ammeter measures current constantly during a treatment session to ensure values are as expected, so that treatment is halted if measurements fall out of the designated range;
- An internal temperature sensor measures temperature constantly during treatment session, so that treatment is halted if measurements fall out of the designated range;
- The generated field intensity decreases with distance in a negative proportion to the cube of the distance from the generating coil, thus, at a distance of 50 cm from the device the power of the generated field is negligible;
- The device is limited by a physical fuse which ensures the device cannot surpass 15 W and reach higher, potentially dangerous, energy levels even in cases of system malfunction;
- Even in cases of device malfunctions the field intensity cannot surpass 7 G;
- The Qompass component Electronics are enclosed in a plastic frame (box) and separated from the user by a foam adhesive preventing direct contact with electronics.
- The Qompass component Battery is certified in compliance with UN 38.3 testing standards.
- The Qompass component uses off-the-shelf medical grade adhesive patches (e.g., 3M products), complying with ISO 10993
- The operators (both at the clinic and at home) are required to undergo an approval process before operating the equipment;
- The IFU contains instructions and warnings for the user to ensure appropriate use and to assist in case of malfunction.
- The risk of falls is mitigated by the use of standard PT/OT exercises and assistance by an approved caregiver (please refer to § 6.1.2) or therapist depending on the subjects' location.
- To mitigate infection, cross-contamination, in this study the fabrics are replaced or disinfected between patients.
- To mitigate and prevent a cybersecurity breach, all communication and entry points are secured (2 factor identification on all interactions between the application and server), no patient or treatment data is stored on the application, minimal non identifying data are stored on the cloud, and the company uses HIPPA complainant cloud and video conference platforms.

In addition, the manufacturer has verified and validated through testing the:

- Device performance in bench testing;
- Device compliance with the basic electronic safety requirements per IEC 60601-1;
- Device compliance with electromagnetic compatibility requirements per IEC 60601-1-2;
- Device software functionality and reliability;

Safety of the BQ 2.0 use during pregnancy, breastfeeding, for individuals with a history of epilepsy or with implanted active electronic and passive MR incompatible devices has not been established, as consequently reflected in the eligibility criteria for this study.

The manufacturer conducted a thorough risk evaluation and assessed the available clinical evidence on use of clinical use of electromagnetic fields, including use of ELF magnetic fields in patients with stroke. The manufacturer also assessed the pharmaceutical and interventional, OT/PT and other modalities available for treatment in the acute and subacute stages of stroke (reflected in §§ 2.1, 2.2, and 2.3.1). The manufacturer conducted several pre-clinical assessments (please refer to § 2.2.1) and a clinical trial with the previous model of the device (please refer to § 2.2.2) in the intended population. Having done that, the manufacturer believes that the risks to which the study participants will be exposed do not exceed the risks associated with use of other solutions described thus far in peer-reviewed sources. Some issues cannot be addressed in a setting other than that of a clinical trial described in this clinical investigation protocol. These include providing an ultimate clinical confirmation of the efficacy of BQ 2.0 and lending further support to confirmation of its safety.

Since this study, conducted as part of the clinical development of BQ 2.0, may support clearance of a device able to reduce disability in adult patients with subacute ischemic stroke, the benefit of this outcome outweighs the risks.

3 OBJECTIVES AND ENDPOINTS

NOTE ON DEFINTIONS: For purposes of registration and reporting to clinical trials registries, in particular, ClinicalTrials.gov, the terms Primary Objectives and Endpoints as used in this section align with the terms Primary Purpose and Outcome Measures in ClinicalTrials.gov, respectively[17]. A description of the study objectives and endpoints is provided in a tabular form below.

Objectives	Endpoints
Primary	
To show that the BQ therapy is effective in reducing global disability at 3 months post-stroke in disabled patients with upper limb motor impairment when initiated 4 to 21 days following an ischemic stroke.	Modified Rankin Scale (global disability) change from baseline (4-21 days post-stroke) to 90 days post-stroke.

[17] For purposes of registration on ClinicalTrials.gov, these are consistent with the definitions in 42 CFR Part 11.10(a) and the provisions of the PHS Act § 402(j)(2)(A)(ii)(I)(cc) and §§ 402(j)(2)(A)(ii)(I)(ll), 402(j)(1)(A)(v), and 402(j)(3)(C)(ii) for Primary Purpose and Primary Outcome Measures, accordingly.

Secondary Efficacy	
To show that the BQ therapy is effective in reducing upper and lower limb impairment, and improving upper limb functionality, health-related quality of life (HRQoL), and level of participation in instrumental activities of daily living (ADL) at 3 months post-stroke, when initiated 4 to 21 days following an ischemic stroke.	The secondary efficacy endpoints will be analyzed in stepwise gatekeeper manner to control for multiplicity. The hierarchical order of analysis will be: 1. Lead secondary endpoint: Fugl-Meyer Assessment for Upper Extremity (upper limb function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 2. Box and Block Test (arm motor function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 3. 10 Meter Walk Test (gait speed) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 4. Stroke Impact Scale Hand Domain (patient-reported hand function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 5. Stroke Impact Scale 16 (patient-reported physical functional limitation) – change from baseline (4-21 days post-stroke) to 90 days post-stroke. 6. 5-level EQ-5D (health-related quality of life) at 90 days post-stroke.

Safety	
- To characterize the safety profile of the BQ therapy. - To show that the BQ 2.0 performs reliably.	- Serious procedure or device related adverse events. - device deficiencies to detect operational reliability.
Tertiary/Exploratory	
- To show that the BQ therapy is effective in reducing cognitive impairment, depression and fine-grained level of disability at 3 months post-stroke, when initiated 4 to 21 days following an ischemic stroke. - To characterize the long-term effect at 6 months post-stroke of the BQ therapy effect on upper limb functionality and health-related quality of life (HRQoL). - To formally evaluate the cost-effectiveness of the BQ therapy over a lifetime horizon from the perspective of the United States healthcare system. - To explore the relationship between adherence to treatment as measured by the Qompass and clinical outcomes	- Montreal Cognitive Assessment (global cognitive function) – at 90 days post-stroke. - Patient Health Questionnaire-8 (depression) – at 90 days post-stroke. - Academic Medical Center Linear Disability Scale (granular level of disability) at 90 days post-stroke. - Modified Rankin Scale (global disability) change from baseline (4-21 days post-stroke) to 180 days post-stroke. - Stroke Impact Scale Hand Domain (patient-reported hand function) – change from baseline (4-21 days post-stroke) to 180 days post-stroke. - 5-level EQ-5D (health-related quality of life) at 180 days post-stroke. - Formal cost-effectiveness analysis over a lifetime horizon from the perspective of the United States healthcare system. - Relationship between adherence to treatment as measured by the Qompass and the clinical outcomes

4 STUDY DESIGN

4.1 OVERALL DESIGN

- Type of trial: prospective, multicenter, double-blind, randomized, sham-controlled, parallel two-arm study following a sample-size–adaptive design with a single planned interim analysis (for details of the interim analysis, please refer to § 9.4.6).
- Statement of hypothesis: improvement in mRS score from baseline to 90 days post-stroke will be greater in patients allocated to active stimulation (BQ 2.0 group) than in patients allocated to sham stimulation (sham) group.

- Sample size and allocation: 150 subjects[18] assigned at 1:1 allocation ratio to either active or sham group.
- Study population: ischemic stroke subjects with upper limb motor impairment.
- Phase: pivotal.
- Number of sites: approximately 20 centers.
- Total enrollment from each site to be no more than 20% of the total sample size.
- Duration for each subject: participation in this study will start at day 3-21 post-stroke and will last up to 180 ± 15 days post-stroke.

NOTE: Sponsor's representative(s) may be present during study interventions, in-person or via combined audio and video remote conferencing or audio only, if video is not available. Presence of the Sponsor during procedures is for observational purposes only and is predicated on the premise of benefit to subject's well-being, as exemplified in the Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products (ATMP) issued by the European Commission https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf.

Despite of its non-binding nature, EU-only application, and non-universal scope, it shows that there are conditions where subject's well-being may benefit from Sponsor's presence and this would not be considered unethical.

According to this guidance, "*The presence of the sponsor (or a representative thereof) during the administration of the ATMP to the clinical trial subject or in any upstream collection procedure is only acceptable if it is duly justified. If such presence is envisaged before the start of the clinical trial, this should be explained in the informed consent. If, exceptionally, the presence of the sponsor (or a representative thereof) has not been foreseen from the outset of the clinical trial but it is justified for reasons related to the protection of the clinical trial subjects or to detect and prevent errors in the extraction of cells/tissues and/or administration, the clinical trial subject should be informed a posteriori. As appropriate and in connection with the enrolment of future patients, the sponsor should submit an amendment to the protocol and an update to the informed consent.*"

Consequently, the fact of possible presence of the Sponsor's representative(s) during the study treatment, to the extent permissible by local laws and regulations, will be described in the informed consent process and detailed in the informed consent documentation, at all sites participating in this study.

[18] May also be referred to as study participants or simply participants in this protocol.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The randomized, double-blind, sham-controlled, trial design has been selected as it is the most rigorous to employ in device trials. Randomization best assures balance between treatment groups in both measured and unmeasured baseline variables. Sham-controlled blinding prevents both patient and rater bias in outcome assessment (72).

Start of study treatment 4-21 days after index stroke allows initiation during the time period of maximal neural reorganization following stroke, as well as assures that patients are medically and neurologically stable at time of entry and are in a well-controlled environment during initial stimulation sessions.

Enrolling patients with moderate-severe disability at baseline assures patients have substantial potential for improvement, minimizing ceiling effects. Patients with upper extremity motor deficits are selected because upper limb motor impairment is a major cause of disability in ischemic stroke patients and upper extremity therapy exercises are performed comfortably by patients when seated within the device.

The modified Rankin Scale was selected as the primary endpoint because it is a measure of global disability and all level changes from 0 to 5/6 are known to be of unequivocal and of substantial value to patients and clinicians. The choice of the Fugl-Meyer Assessment for Upper Extremity as the lead secondary endpoint adds a focused evaluation of the leading target for improvement – upper limb function.

4.3 JUSTIFICATION FOR DOSE

Not applicable.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA; § 1.3). The end of the study is defined as completion of the last visit shown in the SoA for the last subject in the trial[19].

[19] 42 CFR Part 11 § 11.10(a)(3) “study completion date”; ISO 14155:2020 § 8.1

The study primary completion date,[20] is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary 90 days outcome, whether the trial concluded according to this protocol or was terminated.

For the purposes of regulatory submissions to support market approval, data through 90 days is intended to support safety and effectiveness and submission is planned when the last subject enrolled is through the 90-day study period. Additional longer-term data is exploratory in nature.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. mRS score of 3 or 4.
2. FMA-UE score between 10-45 (inclusive) of impaired limb.
3. Age 22 to 85 years of age (inclusive).
4. Diagnosed with an ischemic stroke, confirmed by CT[21] or MRI[22] imaging.
5. Four to 21 days from stroke onset (or last known well).
6. Pre-stroke mRS of 0 or 1.
7. Able to sit with the investigational device for 40 consecutive minutes, in the opinion of the investigator or designee.
8. Can follow a 3-step command, such as “take the paper, fold it in half, and return it to me”.
9. Willingness to participate in occupational/physical therapy activities during study intervention sessions.
10. Availability of a relative or other caregiver able to assist during PT/OT treatment, and to operate an application installed on a mobile device, including a video call.
11. If female, not pregnant (as confirmed by a urine or a blood test, or as determined by an official medical document) or breastfeeding and with no ability to become pregnant or on an acceptable method of contraception during the study
12. Informed consent signed by subject (if competent) or legally authorized representative.

[20] 42 CFR Part 11 § 11.10(a)(3) “completion date” or “primary completion date” synonymous to the “completion date” defined in section 402(j)(1)(A)(v) of the Public Health Service Act [42 U.S.C § 282(j)(1)(A)(v)]
[21] Computed tomography
[22] Magnetic resonance imaging

5.2 EXCLUSION CRITERIA

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

1. Severe neglect impairment (NIHSS item 11, score = 2) or neglect that is severe enough to interfere with reasonable performance of study procedures.
2. Implanted active electronic or passive MR-incompatible devices.
3. Previous ischemic or hemorrhagic stroke within 2 weeks before the index stroke.
4. Pre-existing neurological condition (eg, Alzheimer's disease, Parkinson's disease, multiple sclerosis, traumatic brain injury, spinal cord injury) or physical limitation that would interfere significantly with the subject's participation in the study and/or confound neurological or functional evaluation.
5. Active epilepsy or currently taking anti-epileptic medication (indicated for the treatment of a seizure disorder), or seizure in the last 5 years
6. Significant visual disturbances that cannot be corrected and that would interfere significantly with the subject's participation in the study and/or confound neurological or functional evaluation.
7. Unstable serious illness/condition (eg, active cancer, severe heart failure, active psychiatric condition) or life expectancy of less than 12 months.
8. A known severe allergic reaction to acrylic-based adhesives.
9. Ongoing alcohol abuse and/or illicit drug use.
10. Participation in another trial that would conflict with the current study or clinical endpoint interference may occur.
11. Employee of the Sponsor.
12. Prisoner.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

NOTE ON POINT OF ENROLLMENT:

1. Screening Phase:
    a. Subjects who consented to participate in the initial study assessments for eligibility will be considered enrolled in the Screening Phase.
    b. As long as done within 4 to 21 days from stroke onset, subjects may be reassessed for eligibility before being deemed screening failure.

c. Any subject who consented but was not randomized for any reason will be deemed a screening failure. Such subject will not be counted towards the planned study sample size.

2. Randomized Phase:
   a. Subjects who had their eligibility criteria verified and were randomized will be considered enrolled.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse event and serious adverse event (SAE).

All participating sites, including ACHs and IRFs, will maintain a screening log that will consist of all consented subjects who were or were not randomized. For each screen failure subject, the log will include: date of consent; informed consent version and language; date of screen failure; and reason(s) for exclusion from the treatment phase of the trial.

Screening log containing details of screen failures, including reasons for such, will be kept in the Investigator Site File (ISF).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment

Publicly available or advertised information:

The trial listing on ClinicalTrials.gov will be publicly accessible to patients and families.

- The Sponsor's website may inform site visitors of the study on the webpage listing past, current, and future studies.
- A study specific website may inform site visitors of the study and its key characteristics.[23]
- The Sponsor's social media accounts may contain a link to the corresponding entry(ies) in the publicly accessible database(s) described above in this section. Social networks may be used to advertise the trial.
- Direct advertising may include newspaper/radio/TV/bulletin boards ads.
- Posters and/or flyers may also be issued to advertise the trial.

[23] www.emagine.care

The advertising activities in the indented list above will only commence following documented approval of IRB of such material.

Optimization of recruitment procedures:

NOTE: The strategies listed below will be implemented unless agreed otherwise with the participating site in a site-specific manual of procedures (MOP).

- Participating Acute Care Hospitals (ACH)
    - Recruitment may begin in the ACH, to ensure identification of all potentially eligible patients, facilitate access to the brain CT and MRI scans performed at the acute care hospital, and to give subjects and families maximal time to reflect on the trial before proceeding to the randomization phase.
    - Study Coordinators at the participating ACH, together with stroke team physicians and discharge planners, will each workday review patients newly planned for discharge to a participating IRF, SNF, outpatient, or to a home setting. Patients identified as potentially eligible based on age and time from index stroke will be approached for study consideration.
- Inpatient Rehabilitation Facilities (IRF)
    - Evaluate subjects consented in a participating ACH for continued study eligibility and progression to the randomization phase
    - Identify, consent and enroll patients admitted from both participating and non-participating ACH
    - Study Coordinators at the IRF will each workday review with rehabilitation physicians and nurses newly admitted ischemic stroke patients. Patients identified as potentially eligible based on age and time from index stroke will be approached for study consideration.

Additional sites may be evaluated in case of slow enrollment or lack of the investigation site compliance with this protocol, GCP, or applicable regulations.

Retention

Strategies to optimize subject retention will include:

- Study staff will make subjects and families feel listened to, valued, and supported throughout by listening to subject/family sentiment (and acting on it).
- After discharge from inpatient facility, further study visits will generally be conducted in the subject's home, to avoid the inconvenience and expense of patient travel to a study site.

- Phone calls, emails, video calls, and/or text message reminders about upcoming appointments may be used to help increase visit attendance and overall trial retention.

Vulnerable subjects

Vulnerable subjects (include, but are not limited to pregnant women, those who lack consent capacity, including the mentally ill, cognitively impaired, children (see note below in this section), employees of the Sponsor, or prisoners [even if a participant becomes a prisoner during the study, in which case his/her participation in the study will be terminated]) will not be enrolled in this study. The only exception may be made for the possibility of enrollment of employees of the sites (the latter will be reflected in the informed consent form). Analogously, patients lacking consent capacity due to emergency situations[24] will not be included.

NOTE ON THE DEFINITION OF "CHILDREN"

The U.S. 21 CFR 56.111 refers to children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons as vulnerable populations. Children are defined in 21 CFR 50.3(o) and 45 CFR 46.402(a) as persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted[25]. However, the age of legal competence differs across jurisdictions (73).

The statute in 21 U.S.C. § 360j(m)(6)(E)(i) and (ii) (incorporating Section 520m(6)E(i) and (ii) of the Federal Food, Drug, and Cosmetic Act [FD&C] Act) defines pediatric patients as age 21 years or younger at the time of diagnosis or treatment and specifies categories of pediatric subpopulations. Further, 21 U.S.C. § 360e-1(a) (Section 515A of the FD&C Act), which requires sponsors of premarket application (PMA) and humanitarian device exemption (HDE) applications and supplements to submit information on pediatric subpopulations and pediatric patients, uses the same definition of "pediatric subpopulations". Accordingly, for medical device, the U.S. FDA interprets the statutory definition of pediatrics as individuals who are 21 years of age or younger.

Consequently, to account for any territory-specific variations in definitions, this study will only enroll subjects who are at least 22 years of age.

For detailed recruitment and retention plan, please refer to the MOP.

[24] For instance, as described in Article 68 of the MDR

[25] 45 CFR Subparts B, C, and D defines vulnerable populations as patients who are racial or ethnic minorities, children, elderly, socioeconomically disadvantaged, underinsured

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The BQ 2.0 (Figure 6) is a medical device that produces and delivers non-invasive, extremely low intensity and frequency (1-100 Hz.; up to 1 G), frequency tuned electromagnetic fields in order to stimulate neuronal networks with the aim of reducing disability and promoting neurorecovery. The technology behind the device technology utilized explanatory machine learning (ML) and Brain-Computer Interface (BCI) tools to identify high-resolution spectral patterns that characterize motor functions; the tools are based on a large database of EEG spectra taken during functional motor tasks. These spectral patterns are then translated into a frequency-tuned, low-intensity and non-invasive electromagnetic field treatment, which applies similar patterns directly to the patient's CNS.

The BQ 2.0 is intended to be used in conjunction with the current standard of care. Treatment with BQ 2.0 includes 45 sessions of 60 minutes. Each session includes 40 minutes of exposure to the BQ therapy. Throughout the session, subjects will be asked to perform a standardized device-guided exercises to further support their recovery process. These exercises will be based on a pre-defined and evidence-based physical and occupational therapy regimen focused on upper and lower extremity rehabilitation, aligned with the Class 1 level A recommendation for patients with stroke to participate in a home-based rehabilitation program.

From a user perspective, the BQ 2.0 is a portable, non-invasive treatment designed to be used in a variety of settings (eg, in a clinical facility or patient's home).

6.1.1.1 DEVICE SIZE(S)

For device dimensions, please refer to the IFU.

6.1.1.2 DEVICE MODEL(S)

- The BQ 2.0. includes three configurations which vary in size to accommodate different individuals based on their physical characteristics.

6.1.1.3 DESCRIPTION OF EACH COMPONENT

To achieve its purpose, BQ 2.0 (Figure 6) comprises the *DEVICE* and the *SOFTWARE APPLICATION* installed on A*NDROID* based *TABLET*:

1. *DEVICE* (Figure 7) – Wearable Device which includes: (1) embedded magnetic coils; (2) Waveform generator; (3) Rechargeable battery; and (4) the Qompass. The magnetic *COILS* are configured in three-dimensional shapes; with one *COIL* in the shape of a rectangle that goes along the spine, and two circle-shaped *COILS* that surround the brain.
   Custom plastic *COMBS* are used to ensure correct placement of the *COILS*. These are secured to a sheet of polypropylene. Also secured to the polypropylene are a custom box containing the printed circuit board which creates the wave function and a custom *BATTERY BOX* containing the battery to power the Device. The entire structure is covered in a layer of fabric which includes a *WAISTBAND* and *SHOULDER STRAPS* to secure the Device to the patient. *THE QOMPASS* (Figure 8) is a single-use sensor designed to be placed on the subject's forehead for the duration of each treatment session via an adhesive. It contains sensors that detect the electromagnetic field that the subject is exposed to, to ensure a subject receives the treatment as intended and allow for in depth monitoring and treatment optimization[26]. Each unit is designed for one-time use to simplify the user experience.

Control of operation of the *DEVICE* is enabled through operation of the

2. *SOFTWARE APPLICATION* v. 5.0 and above (Figure 9) – (Android; Transmission Control Protocol/Internet Protocol (TCP/IP) communication), installed on an Android-based mobile device. The *SOFTWARE APPLICATION* controls the functionality of the *DEVICE*. Data collected is uploaded to a cloud compliant with the Health Insurance Portability and Accountability Act (HIPAA; implemented in 45 CFR Part 160 and Part 164, Subparts A and C) and the General Data Protection Regulation (GDPR; Regulation (EU) 2016/679). Data upload is performed strictly for backup purposes. No data interpretation is conducted on the cloud.

The *SOFTWARE APPLICATION* does not require entry of any patient-identifying information into the device, nor connecting the device to hospital data systems, eg, electronic medical record (EMR). To use the device, a system administrator must create an account for each user to login (Figure 9). Existing patients can be selected from the patient selection screen by authorized caregivers or operators (Figure 10). Overview of the upcoming treatment is then presented (Figure 11). Treatment screen is presented following treatment initiation (Figure 12).

[26] In the clinical trial setting the data will only be collected, will not be accessible to blinded personnel or participants and will not be used to actively monitor and optimize the dosage in order to maintain the blinding.

For the exhaustive description and operational instructions of BQ 2.0, please refer to the IFU.

Figure 6. BQ 2.0 – overview

Figure 7. BQ 2.0 – *DEVICE* components

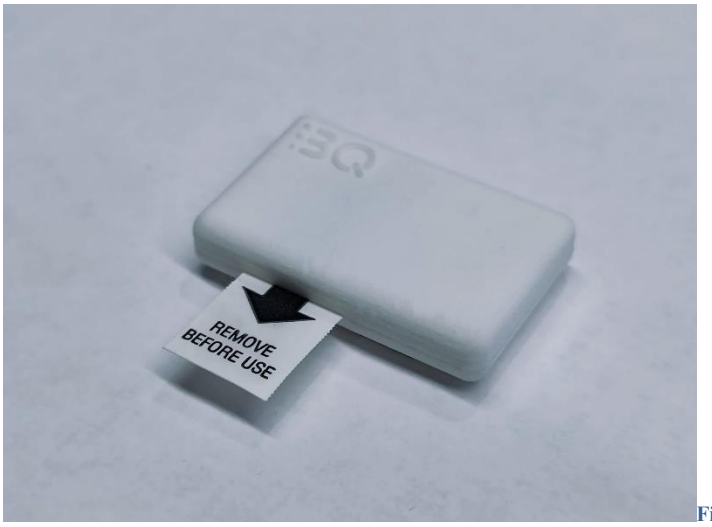


Figure 8. The Qompass

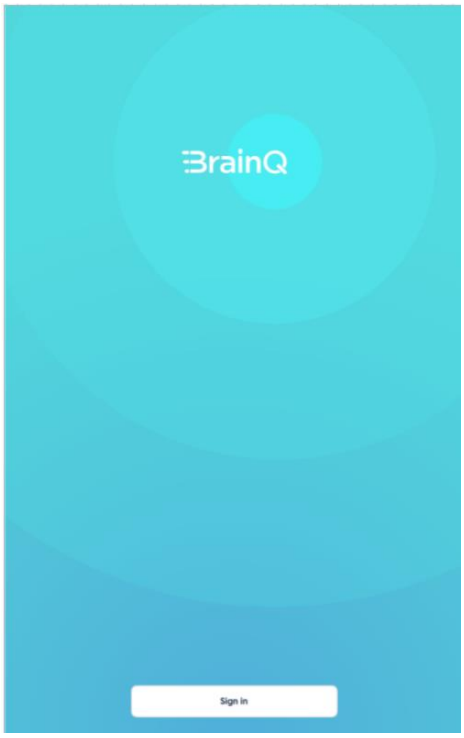


Figure 9. BQ 2.0 *SOFTWARE APPLICATION* sign in screen

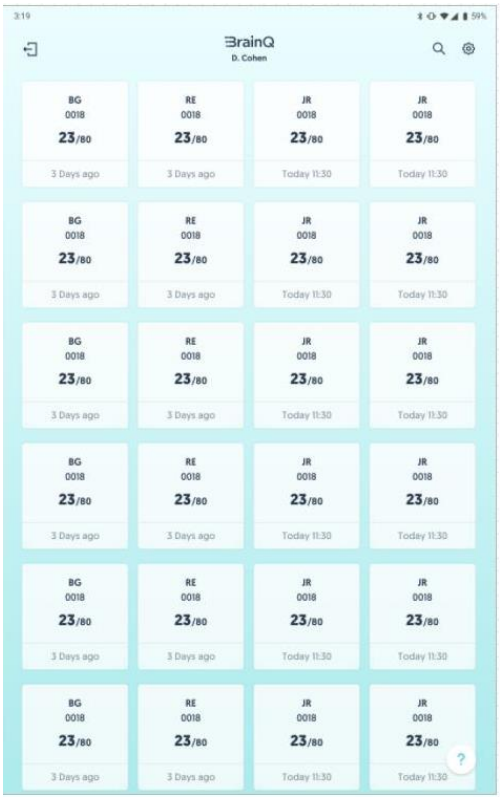


Figure 10. BQ 2.0 *SOFTWARE APPLICATION* patient selection screen

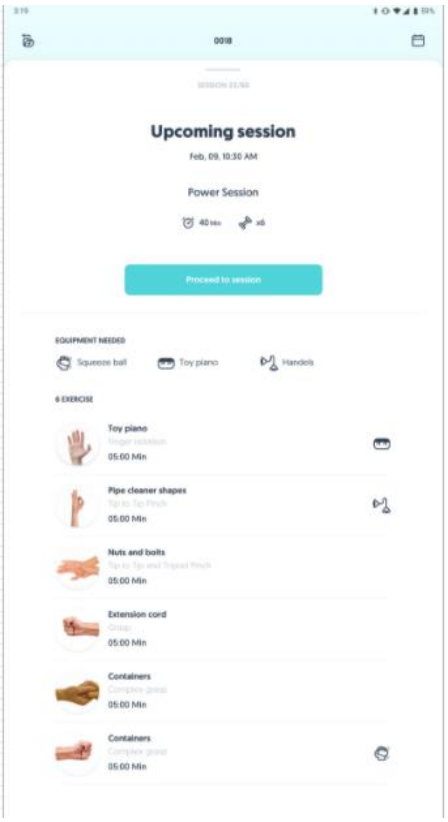


Figure 11. BQ 2.0 *SOFTWARE APPLICATION* treatment overview screen

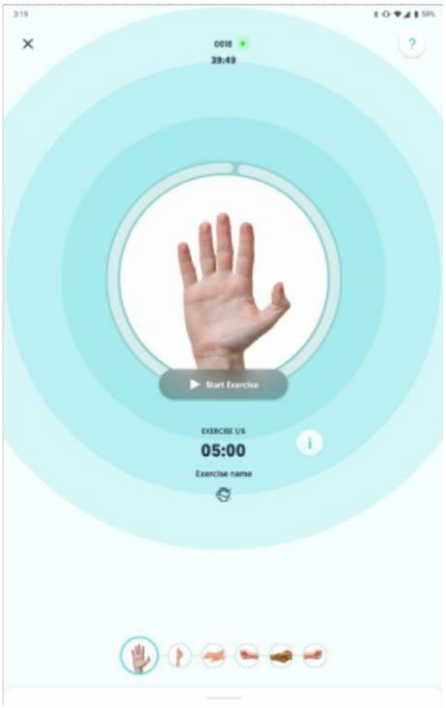


Figure 12. BQ 2.0 *SOFTWARE APPLICATION* treatment screen

6.1.1.4 DURATION OF EXPOSURE

The maximal exposure to BQ 2.0 stimulation during a treatment session is 40 consecutive minutes.

6.1.1.5 FREQUENCY OF EXPOSURE

The BQ 2.0 will be used 5 times a week to a total of 45 treatment sessions in each subject.

6.1.1.6 SUMMARY/REPORT OF TEST VALIDATION STUDIES

For summary of test validation studies please refer to the IFU.

6.1.2 DOSING AND ADMINISTRATION

Randomized patients will receive active or sham study intervention sessions using BQ 2.0 (active or sham therapy, respectively), starting 4-21 days after stroke onset and no later than 2 days after randomization. Sessions will be conducted 5 times a week. Each session will last up to 60 minutes, with active or sham field being turned on for up to 40 minutes. The only difference between the BQ 2.0 active stimulation and sham therapy is that the sham device does not generate electromagnetic fields during treatment. Subjects in both the active intervention group

(BQ 2.0 group) and sham group will be asked to perform trial-specified physical and occupational therapy activities during each session, in addition to their standard care rehabilitation therapies.

During the study, 45 sessions of active or sham therapy will be conducted in either inpatient, outpatient or home setting.

. A trained member of the site study team (the "**Clinic Operator**") will be responsible for training and approving the subject's caregiver to operate the session independently.

Before an approval to operate a session independently (the "**Approval**") is granted by the Clinic Operator, a Clinic Operator will train the caregiver and supervise the sessions, either in-person or remotely. Once an Approval was granted, sessions will be conducted with the assistance of a caregiver while the Clinic Operator will provide periodic oversight (combined audio and video remote conferencing or audio only, if video is not available). If needed, and at their discretion, the Clinic Operator may join sessions following the Approval too.

A complete session is one which includes at least 40 minutes of stimulation. For each treatment session, after the initiation of the stimulation, a pause in or early cessation of stimulation after the initiation of the stimulation, should be avoided as much as possible. If the stimulation is paused, the session may be reinitiated within 30 minutes. Additional pause before the stimulation is complete (or before 30 minutes of stimulation have been complete in the first 5 occurrences) will result in session termination. If over 30 minutes of stimulation have been completed but the stimulation was stopped before completion, in the first 5 occurrences – the session will be considered complete. Subsequent shortened sessions will be considered incomplete. Missed or incomplete treatment sessions will be rescheduled until 45 treatment sessions are completed. Rescheduled sessions will not result in having over 5 treatment sessions administered in a week. Instead, this will extend the total number of weeks required to complete 45 sessions. Treatment sessions can be completed until the day before the Day 90 follow-up visit. Missed treatments won't be considered as Protocol Deviation as long as rescheduled and completed within the allowed window (until the day before the 90 Day (±15) follow up visit).

For treatment schedule disruptions that will lead to subject withdrawal from the study, please refer to § 7.2.

6.1.3 CONTROL INTERVENTION DESCRIPTION

Sham intervention is identical to BQ 2.0 therapy, except that no electromagnetic energy is generated by BQ 2.0. Other than that, all provisions of § 6.1.1 apply here as well.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Investigators will administer study device only to subjects included in this study and following the procedures set out in this protocol. All study devices must be accounted for throughout the study using accountability logs. Investigators must maintain accurate and adequate records, including dates, serial number, quantities received (if applicable), expiry date, inventory, and individual usage. These records will be verified by the study Monitors during site visits.

For information on procedures and particular materials (eg, packaging materials) and instructions for the safe return of investigational devices, including those that are potentially hazardous, please refer to the study MOP.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Please refer to the IFU for detailed descriptions.

6.2.2.1 STUDY DEVICE

The BQ 2.0 (active and sham), as provided by the Sponsor for this study, comprises a single package including the *DEVICE,* BQ 2.0, and its accessories, including the *SOFTWARE APPLICATION* installed on an Android-based mobile device and approximately 50 units of the *QOMPASS*, packaged and transported in a custom-made packaging. The packaging is made of fabric and mounted to a wheel system to allow for carrying by hand or wheeling of the device. The packaging includes custom bags and compartment for the BQ 2.0 accessories. Foam padding in the BQ 2.0 packaging maintains the device structure and protects it from damage.

6.2.3 PRODUCT STORAGE AND STABILITY

BQ 2.0 shall be stored in designated packaging in accordance with the requirements specified in the IB.

6.2.4 PREPARATION AND HANDLING

Each BQ 2.0 device will be tested prior to allocation to a study participant.

Upon the completion of all study treatments, in coordination with the site and the study participant, the BQ 2.0 shall be collected and sent to a location designated by the Sponsor or to

the site, for cleaning and refurbishment as described below. A designated Sponsor's representative or study team member will complete the following tasks:

1. Replace all fabrics which can come in contact with an individual to avoid cross contamination
2. Inspect the device thoroughly to ensure all of the components are intact and do not have any visual damage
3. Reset the SW application to allow for a new user to use the application with his/her credentials
4. Test the entire set up by performing a treatment session simulation

For complete product cleaning instructions please refer to the MOP.

Only upon the successful completion of all refurbishment and cleaning tasks shall the device be deemed suitable for reuse on a future study participant.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 ALLOCATION TO STUDY INTERVENTION

After informed consent has been elicited from the subject or his/her legally authorized represented, and the subject is determined to fully meet the study eligibility criteria, he/she will be equally allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a permuted block randomization scheme with blocks stratified by site, age (22-69, 70-85) and mRS score at baseline (3 vs 4):

- BQ 2.0 active stimulation group
- BQ 2.0 sham stimulation group

Allocation (randomization) of participants to study groups will proceed through the use of the EDC system (Syncrony) for randomization and the BQ 2.0 Administrator Panel for treatment allocation. The site personnel (Study Coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a group assignment and randomization number. The Syncrony system will provide to the unblinded site personnel the study intervention allocation assigned. The randomization schedule and treatment arm assignments will be kept by Syntactx-NAMSA data manager with appropriate security measures and access control.

6.3.2 BLINDING OF SITE PERSONNEL AND SUBJECTS

This is a double-blind study, subjects and Investigators will be blinded to the device setting (Active/Sham). The study site team members receiving, storing, dispensing, preparing, and administering the study interventions will be blinded. Subjects' caregivers will also be blinded. There are no differences in the active and sham device appearance. Due to the non-invasive nature of the treatment, as well as the physical characteristic of the EMF, there is no noticeable difference between sessions conducted using an active or a sham device, facilitating full blinding of both subjects and Investigators.

BQ 2.0 does not produce any noticeable sound, light or sensation in connection with the stimulation which may disclose the arm assignment, making it ideal for testing in a sham-controlled setup. During sham treatment sessions, for purposes of maintaining the blind, the device will function as if it is delivering the therapy (i.e., the device will turn on and all indicators will function), but the frequency and intensity parameters that are not visible to the subject or site study members will be set to zero so that no stimulation is delivered. Furthermore, in the clinical trial setting, the data collected via the Qompass component of the device will not be accessible to blinded personnel or participants or used to actively monitor or optimize the dosage in order to maintain the blinding.

An authorized un-blinded individual at the site will be the only person to receive the group assignment of the randomized subject, and will enter the subject's group assignment to the study device, in accordance with the IFU and/or training received from the Sponsor. For more information, please refer to the Blinding Plan.

6.3.3 BLINDING OF THE SPONSOR

The Sponsor, the sites and the study statistician will remain blinded throughout the study. This blinding will include the interim analysis results as well; only the decision made will be shared. An independent unblinded statistician (not the study statistician) will perform the assessments for the interim analysis. An unblinded representative of the Sponsor may be designated as well.

For unblinding procedures in place for the planned interim data analysis, please refer to § 9.4.6. as well as to the Unblinding Plan.

6.3.4 BREAKING THE BLIND

The randomization schedule and treatment arm assignments will be kept by Syntactx-NAMSA data manager with appropriate security measures and access control. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's study intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the

Investigator should make every effort to contact the Sponsor prior to unblinding a subject's group assignment, unless this could delay further management of the subject. If a subject's group assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and communicated to the sponsor in a formal communication medium.

6.4 STUDY INTERVENTION COMPLIANCE

Following intervention, appropriate CRF must be filled in, within the time frame for completion as specified in Table 5. The date and time of each treatment administered will be recorded in the source documents and recorded in the CRF. The study Monitor will check the CRF against the accountability log and related treatment session worksheets used by the site to verify the number of devices dispensed on a per-subject basis.

6.5 CONCOMITANT THERAPY

All sites will provide concomitant medical therapies to prevent recurrent stroke and conventional rehabilitation therapy to maximize recovery from the index stroke according to United States national guidelines (43, 74, 75).

All concomitant prescription medications, over-the-counter medications, and supplement medications taken during study participation will be recorded on the appropriate CRFs. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Any symptoms of treatment-emergent clinical deterioration in subject's condition requiring intervention of the medical team to alleviate these symptoms and qualifying for toxicity Grade 3 (or higher) on the CTCAE v.5.0 scale will result in a halt of administration of the study intervention for that treatment session; halting for a longer period of time will occur only if deemed necessary by the Investigator.

In general, discontinuation of administration of the study intervention, for any reason, does not mean discontinuation from the study, and the remaining study procedures should be completed as indicated by the study protocol, unless informed consent is withdrawn. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the Investigator or qualified designee will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an AE. For requirements on reporting of adverse events, serious adverse events and unanticipated problems please refer to §§ 8.3.5, 8.3.6, and 8.4.2, respectively.

The data to be collected at the time of discontinuation of administration of the study intervention will include the date and reason for discontinuation and any data on the adverse event(s), if applicable.

Women who become pregnant during the trial will continue to be assessed, including assessment of pregnancy outcomes, and investigational device administration will be discontinued. Further provisions on reporting of pregnancy, including period of reporting are in § 8.3.9.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study or discontinue the study intervention at any time upon request. Those wishing to discontinue participation do not have to provide a reason; however, when appropriate, the site investigator should discuss the study, informed consent, and any on-going risks and benefits to continued participation with the participant.

In addition to discontinuation of administration of the study intervention (section 7.1), subject participation in the study may be terminated by the Investigator or the Sponsor if any one or more of the following conditions are met:

- occurrence of an unexpected serious adverse event;

- pregnancy;
- loss to follow-up (refer to § 7.3 for accompanying instructions); health conditions that require treatment that might affect the procedure and/or its outcome;
- significant protocol deviation (please refer to § 10.1.10) or noncompliance, either on the part of the subject or Investigator. These will include (but not limited to):
    - enrollment in violation of the study eligibility criteria;
    - performing the trial procedure not as prescribed in the BQ 2.0 IFU;
    - other ethical or clinical considerations at the discretion of Investigator.
    - enrollment in another interventional study overlapping with the period of participation in this study.

Data collected prior to withdrawal of consent will remain in the study database, but no further data will be collected on those who withdraw. Follow up on serious adverse events that are not resolved by the time that the subject leaves the study will be handled as defined in § 8.3.4. Follow up on pregnancy outcome will be handled as defined in § 8.3.9.

Withdrawn/discontinued randomized subjects will not be replaced.

If a subject withdraws from the clinical investigation, the reason(s) shall be recorded. Withdrawals will be recorded, analyzed, and reported to local IRBs/ECs as required.

7.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he/she fails to attend a scheduled study Visit (including treatments) and cannot be contacted by the study site staff, subject to the completion of the action detailed below:

- Within 2 days from the original missed study Visit, the site will attempt to contact the subject and reschedule the missed visit. The site will counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant and his/her caregiver/s (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods, a visit to subject's last known address where reasonable). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The order of and timeline of the screening procedures and evaluations (Visit 1) are presented in the study schema (please refer to § 1.2) and the schedule of activities (please refer to § 1.3).

The questionnaires and functional tests detailed below are appended to this protocol (please refer to § 12.1).

mRS (first screening procedure after consent is obtained)

The mRS is a 7-level scale with possible scores ranging from 0 (no symptoms at all) through 5 (severe disability) and 6 (death) and is used for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability (76). The mRS is the most frequently used outcome measure in stroke trials (77). To increase outcome comparability and minimize bias, the modified Rankin Scale assessments of global disability will be obtained at all sites using the formal, algorithmic Rankin Focused Assessment-Ambulatory (RFA-A) method by RFA-A-certified raters (78-80). The formal RFA-A elicitation technique is an NIH trial-developed method for assigning mRS scores validated to improve inter-rater reliability in assigning mRS scores. In addition, the RFA-A method to assign mRS scores has been employed for primary and second endpoint ascertainment in numerous FDA-regulated drug and device trials (47, 81-83).

Fugl-Meyer Assessment-Upper extremity (FMA-UE; second screening procedure)

The Fugl-Meyer Assessment is a stroke-specific, performance-based impairment index. It is designed to assess motor functioning, balance, sensation and joint functioning in patients with post-stroke hemiparesis (84, 85). It is frequently applied clinically and in research to determine disease severity, describe motor recovery, and to plan and assess rehabilitation treatment (86). This test is one of the most used instruments in rehabilitation and its validity and reliability has established validity, reliability, and sensitivity to treatment-related change (84, 87, 88).

In this study, the index will be used to assess the motor impairment of the upper extremity after stroke. Each movement will be graded on a 3-point scale, and the total score will range 0–66 points ,with a higher score representing more active movements.

Box and Block Test (BBT)

The Box and Block Test is a quick and simple test which measures unilateral upper extremity function (89). In the BBT, one hundred and fifty 2.5-cm^3 wooden blocks in many different orientations are placed on the side of the partition with the testing hand. A subject's score is equal to the number of these blocks transported over a 15.2-cm–tall partition in one minute. The subject can select blocks in any order to transport over the partition as quickly as possible, with the only requirement being that the subject's fingertips cross the vertical plane of the partition (90).

Stroke Impact Scale (SIS) Hand-Domain and SIS-16

The Stroke Impact Scale is a patient reported outcome instrument designed to assess physical function in patients with stroke. This outcome measure developed in the United States by Duncan et al (91, 92) and has undergone considerable validation and development. The SIS was designed for in-person use, but can be administered via phone or mail, too. The SIS Hand-Domain (SIS version 3.0) assesses hand function, including activities dependent upon grip, pinch strength, and finger dexterity (93).

The SIS-16 assesses physical function, including activities dependent upon upper extremity, lower extremity, trunk, and gait motion (94).

EQ-5D-5L

The EuroQol-5 Dimension (EQ-5D), developed in 1990, is a widely used generic tool to measure generic health-related quality of life (HRQoL) using three levels of severity in five dimensions (95). In 2009, the EuroQol Group developed a new EQ-5D version to overcome limitations related to its consistently reported high ceiling effect. To enhance the sensitivity for assessing HRQoL in further patient populations, the number of responses for each section of the EQ-5D was increased from 3 to 5 levels (EQ-5D-5L; (95)). EQ-5D scores can be converted to patient-specific health utilities that are used in the calculation of quality-adjusted life years and evaluating the cost-effectiveness of medical therapies.

10-meter walk test (10MWT)

The 10-meter walk test is a simple assessment to measure locomotor capacity in clinical and research settings. The individual walks alone or with assistance of no more than one person and their gait velocity is quantified. Assistive devices which are normally used for balance and/or stability (eg, cane or walker) are allowed. Individuals are requested to walk the said distance in their usual or normal pace. The mean velocity of gait has been termed the sixth vital sign (96) because of its very high clinical, research, and real-world relevance.

Academic Medical Center Linear Disability Score (ALDS)

The Academic Medical Center Linear Disability Score is a generic item bank that measures the disability status of patients with a broad range of diseases, as expressed by the ability to perform activities in daily living (97). Using the ALDS, disability level can be quantified in a granular fashion on a continuous scale, using ~15 items tailored to the particular general functional level of each patient.

MoCA

The Montreal Cognitive Assessment is a widely used screening assessment for detecting cognitive impairment developed in Montreal Canada. It is a one-page, 30-point test administered in approximately 10 minutes (98).

PHQ-8

The Patient Health Questionnaire (PHQ) is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders (99). The PHQ-8 is composed of 8 items that assess for depression based on DSM-IV criteria, with each item rated between “0” (not at all) to “3” (nearly every day) (99). The PHQ is an instrument for making criteria-based diagnoses of depressive and other mental disorders commonly encountered in primary care. The PHQ-8 does not include the ninth item of the PHQ-9, as that item has been found not to be reliable and the PHQ-8 performs comparably to the PHQ-9. The PHQ-8 is half the length of many other depression measures, has comparable sensitivity and specificity (99). The PHQ-8 is more efficient than “2-step” depression measures for which, when scores are high, additional questions must be asked to establish DSM-IV depressive diagnoses. Specifically, the diagnostic validity of the PHQ in post-stroke patients has been established in several studies (102-110).

8.1.1 STUDY VISITS

8.1.1.1 PRE-SCREENING PHASE

Prospective subjects, who are 3 to 21 days post-stroke, can be consented to participate in the study at a participating initial acute care hospital (ACH) prior to anticipated discharge to a participating IRF, SNF, outpatient, or home setting. Alternatively, prospective subjects, who are 3 to 21 days post-stroke, can be consented at a participating IRF, SNF, outpatient, or home setting.

Only brief eligibility review to determine initial eligibility and interest in the study will be performed prior to elicitation of consent.

8.1.1.2 SCREENENG & ENROLLMENT, BASELINE VISIT

Efforts should be made to complete enrolment, randomization and initiate treatments as early as possible within the window of recruitment, and target to complete a first treatment within 4 weekdays from admission to the participating site.

For consented subjects, the following additional data will be recorded at this visit:

- Demographics – age, sex, race/ethnicity
- Medical history - presence of concomitant medical conditions (eg, hypertension, diabetes, hyperlipidemia, atrial fibrillation, prior ischemic stroke, prior hemorrhagic stroke, current or past smoking)
- Vital signs – temperature, pulse, blood pressure.
- Concomitant medications – any concomitant medications by or administered to the subject at the time of screening (for details, refer to § 6.5).
- In women of childbearing potential a urine or blood test will be performed unless there is a documentation of a negative pregnancy test in an official medical documentation.
- mRS
- FMA-UE,
- BBT,
- 10MWT
- SIS Hand Domain,
- SIS-16,
- SAFE
- NIHSS
- Any adverse events

Consented subjects, who are 4 to 21 days post-stroke, and have passed screening for eligibility will advance to the treatment phase of the study, commencing with randomization.

Randomization should be performed within 24 hours from the mRS and FMA-UE assessments. If more than 24 hours have elapsed, these assessments should be repeated and only those subjects whose reassessed scores for both assessments conform with the eligibility criteria will be randomized. The later scores will serve as the baseline scores and for stratification.

Eligible subjects will be randomly assigned, at a 1:1 allocation ratio, to either the active or sham study intervention groups.

The following additional data will be obtained after randomization and not later than Midterm follow-up visit:

- Imaging Data – there will be no imaging tests performed in the study. However, for subjects randomized to the study, all computed tomography (CT), CT angiography (CTA), CT perfusion (CTP), and brain magnetic resonance imaging (MRI) perfusion/diffusion-weighted imaging (DWI/PWI) / fluid attenuated inversion recovery brain magnetic resonance angiography (FLAIR), and brain magnetic resonance angiography (MRA) studies available from the first 7 days in the ACH will be transferred to the sponsor by either using CD's or via an online cloud based service. If multiple images are available from different recording sessions at the acute stay, it is required to collect the first image and the last image[27]. Please refer to the study MOP for instructions.
- The following values from the complete blood count performed at the time the subject was admitted and diagnosed with stroke will be transcribed into the CRF:
    - red blood cell distribution width (an independent predictor of 3-month functional outcome; (111))
    - absolute white cell count (an independent predictor of stroke severity and degree of disability; (112))

8.1.1.3 TREATMENTS 1-20

Randomized subjects will undergo the first treatment session no later than 48 hours after randomization and within 4-21 days after stroke onset. Active or sham study intervention sessions using BQ 2.0 (active or sham therapy, respectively) will be conducted 5 times a week, for approximately 9 weeks and until completion of 45 treatment sessions, conducted in either inpatient, outpatient or home setting.

At each of these visits, the subject will undergo a study treatment. Each treatment session will last up to 60 minutes, with active or sham field being turned on for the first 40 minutes. During the session, subjects will be asked to perform a device guided, standardized, pre-defined and evidence-based PT/OT therapy activities, with approximately 30 minutes dedicated to the upper extremity and 30 minutes to the lower extremity, aligned with the Class 1 level A recommendation for patients with stroke to participate in a home-based rehabilitation program.

A trained member of the site study team (the "**Clinic Operator**") will be responsible for training and approving the subject's caregiver to operate the session independently.

[27] MRI images will be preferred over CT images

Before an approval to operate a session independently (the "**Approval**") is granted by the Clinic Operator, a Clinic Operator will train the caregiver and supervise the sessions, either in-person or remotely. Once an Approval was granted, sessions will be conducted with the assistance of a caregiver while the Clinic Operator will provide periodic oversight (combined audio and video remote conferencing or audio only, if video is not available). If needed, and at their discretion, the Clinic Operator may join sessions following the Approval too.

At each of these visits, the following data will be collected:

- Any changes in concomitant medications
- Any adverse events
- Any device deficiencies
- Duration of stimulation delivered and number of pauses if occurred
- Duration of PT/OT activities performed during the 60-minute period
- PT/OT activities performed outside of study since last visit

8.1.1.4 MIDTERM FOLLOW-UP VISIT (IN CLINIC)

This visit will take place in the clinic (±4 days from the 20th treatment). Though, in special circumstances and subject to the approval of the Principal Investigator, the visit can be conducted in an out-patient setup or via combined audio and video remote conferencing or audio only, if video is not available.

The following assessments (described in § 8.1) will be performed during this visit:

- mRS,
- FMA-UE,
- BBT,
- SIS Hand Domain,
- SIS-16

At this visit, the following data will be collected as well:

- Vital signs
- Any changes in concomitant medications
- Any adverse events
- Any device deficiencies
- PT/OT activities performed outside of study since last visit
- Use of healthcare resources

At this visit day, a treatment session may or may not take place, in accordance to the availability of the subject and/or the site. If a session will not take place, and unless completed over the weekend, 4 treatment sessions will take place in that week.

If a treatment session is to take place at the same day of the assessment, the session may be conducted only after the assessments were completed to avoid changing outcome measure scores due to subject fatigue.

8.1.1.5 TREATMENTS 21-45

At each of these visits, the subject will undergo a study treatment. Each treatment session will last up to 60 minutes, with active or sham field being turned on for the first 40 minutes. During the session, subjects will be asked to perform a device guided, standardized, pre-defined and evidence-based PT/OT with approximately 30 minutes dedicated to the upper extremity and 30 minutes to the lower extremity aligned with the Class 1 level A recommendation for patients with stroke to participate in a home-based rehabilitation program.

At each of these visits, the following data will be collected:

- Any changes in concomitant medications
- Any adverse events
- Any device deficiencies
- Duration of stimulation delivered and number of pauses if occurred
- Duration of PT/OT activities performed during the 60-minute period
  PT/OT activities performed outside of study since last visit

8.1.1.6 DAY 90 PRIMARY OUTCOME ASSESSMENT VISIT (IN CLINIC)

This visit will take place in the clinic. Though, in special circumstances and subject to the approval of the Principal Investigator, the visit can be conducted in an out-patient setup or via combined audio and video remote conferencing or audio only, if video is not available.

The following assessments (described in § 8.1) will be performed during this visit:

- mRS,
- FMA-UE,
- BBT,
- 10MWT
- SIS Hand Domain,
- SIS-16,

- EQ-5D-5L
- ALDS,
- MoCA,
- PHQ-8,

At this visit, the following data will be collected:

- Vital signs
- Any changes in concomitant medications
- Any adverse events
- Any device deficiencies
- PT/OT activities performed outside of study since last visit
- Use of healthcare resources

Additionally, at this visit, the subjects will be asked to rate their certainty regarding group allocation by selecting one of five options: (1) knew they had received active stimulation; (2) thought they received active stimulation; (3) knew they were in the sham stimulation group; (4) thought they were in the sham stimulation group; or (5) did not know which treatment group they were allocated.

8.1.1.7 DAY 180 ADDITIONAL FOLLOW-UP VISIT

This additional follow up will be conducted remotely via combined audio and video remote conferencing (or audio only, if video is not available), or in-person, if preferred.

The following assessments (described in § 8.1) will be performed during this visit:

- mRS
- SIS Hand Domain,
- EQ-5D-5L

At this visit, the following data will be collected:

- Any adverse events
- Any changes in concomitant medications
- Use of healthcare resources

8.2 SAFETY AND OTHER ASSESSMENTS

The following procedures/evaluations will be performed to assess safety in this study in addition to the descriptions already described above in this § 8.

Assessment of adherence to investigational product use. Please refer to § 6.4.

Assessment of adverse events. Adverse events will be assessed for severity, seriousness, expectedness, action taken, and relation to the study device and procedure and recorded at each study Visit, at which time the subject will provide data on all adverse events that occurred since the last Visit. Please refer to §§ 8.3.1, 8.3.4, 8.3.5, and 8.3.8 for adverse event definitions, period of reporting, reporting specifications, and events of special interest.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. This definition includes events related to the investigational medical device or the comparator[28]. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical device or comparators.

AEs include any event having been absent at baseline, or, if present at baseline (medical history), subsequently worsening.

Adverse device effect (ADE) is an adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error[29]

[28] Comparator is a medical device, therapy (eg, active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation (ISO 14155:2020 § 3.12)

[29] ISO 14971:2019 (definition 3.30): user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Use error includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered use error. A malfunction of a medical device that causes an unexpected result is not considered a use error.

or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device.

Device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, *usability*, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. *This definition includes device deficiencies related to the investigational medical device or the comparator*.[30]

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious adverse event (SAE) is an adverse event that that led to any of the following

a. death,
b. serious deterioration in the health of the subject, *users or other persons* as defined by one or more of the following:
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function including chronic diseases, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c. fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation protocol, without serious deterioration in health, is not considered a serious adverse event.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

[30] The part of the device deficiency definition appearing in italics is introduced in ISO 14155:2020 and is absent from the definition available in CHAPTER I Article 2(59) of the MDR. For the purposes of this trial, the definition in this protocol will apply for Investigator reports to the Sponsor. Applicability of the gap between the definitions in this protocol and the aforementioned MDR definition will be assessed for Sponsor reports to National Competent Authorities if and where MDR will apply to this trial.

8.3.3.1 SEVERITY OF EVENT

All events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 available on:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Grade refers to the severity of the AE. The CTCAE v.5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for certain AEs based on a general guideline shown in Table 3 below.

Table 3. NCI CTCAE v.5.0 grading system

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening;	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences	Urgent intervention indicated.
Grade 5	Death related to AE.	

*Instrumental ADL (Activities of Daily Living) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For events not listed in the CTCAE toxicity table, severity should be assessed using the general CTCAE grading guideline provided in Table 3.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the Investigator who examines and evaluates the subject will provide the Sponsor with his/her assessment of the AE causality based on temporal relationship and his/her clinical judgment[31]. The degree of certainty about causality will be graded using the categories in Table 4 below[32].

[31] Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events (MEDDEV 2.7/3 revision 3 - GUIDELINES ON MEDICAL DEVICES - CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)

[32] Based on the EU medical device coordination group (MDCG) guidance 2020-10/1 *Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745.* Although originally proposed for serious adverse events, it is suitable for non-serious events as well.

The Sponsor and the Investigators will distinguish between the serious adverse events related to the investigational device, those related to the procedures (any procedure specific to the clinical investigation), and those unrelated to either the investigational device or study procedures. An adverse event can be related both to procedures and the investigational device.[33]

Table 4. Causality of adverse events

Not related	Relationship to the device, comparator or procedures can be excluded when: – the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device; – the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; – the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event; – the event involves a body-site or an organ that cannot be affected by the device or procedure; – the serious adverse event can be attributed to another cause (eg, an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); – the event does not depend on a false result given by the investigational device used for diagnosis[34], when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal relationship	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: – the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

[33] Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

[34] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer) or might not be diagnosed with the correct disease or condition.

	– the event has a temporal relationship with investigational device use/application or procedures; – the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; – the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); – the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); – other possible causes (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; – harm to the subject is due to error in use; – the event depends on a false result given by the investigational device used for diagnosis[35], when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation. The Sponsor or Sponsor's designee (Medical Monitor/Expert[36]) shall review the Investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device and the procedure; in case of disagreement between the Sponsor and the Investigator(s), BrainQ Technologies Ltd. shall communicate both opinions to concerned parties[37] (refer to § 8.3.6 for details on reporting of serious adverse events), unless otherwise instructed by a local regulation or guidance.

[35] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition

[36] Clinical Data Interchange Standards Consortium (CDISC) glossary item C51836 defines Medical Monitor as "A sponsor representative who has medical authority for the evaluation of the safety aspects of a clinical trial." The US FDA Compliance Program 7348.810 BIORESEARCH MONITORING Guidance for FDA Staff on "SPONSORS, CONTRACT RESEARCH ORGANIZATIONS AND MONITORS" (April 2017) clarifies that Medical Monitor may have the responsibility for
medical aspects of the study (and may be a physician) while other Monitors may assess regulatory compliance.
ICH GCP E6(R2) defines medical expert as medical personnel who will be readily available to advise on trial related medical questions or problems.
ISO 14155:2020 notes that medical expertise is provided by a person qualified by education, training and experience, who is readily available to advise on the clinical investigation and related medical questions or problems. If necessary, outside consultant(s) can be available for this purpose.

[37] § 8.2.5(a) of EN ISO 14155:2011/AC:2011 and § 9.2.5(a) of ISO 14155:2020, and MEDDEV 2.7/3 revision 3

8.3.3.3 EXPECTEDNESS

Risk analysis conducted by BrainQ Technologies Ltd. shall be used as a basis for identifying anticipated AEs/ADEs characterized by their nature, incidence, severity, and outcome. In general, an AE/ADE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the investigational device. The potential expected (anticipated) side effects, based on the risk analysis, are listed in § 2.3.1 above.

SAEs known to occur with a frequency >1% in the normal course of patients with acute ischemic stroke under standard medical management will generally be rated as attributable to the subject's underlying condition (please refer to the list provided as an appendix to the MOP).

For reporting to regulatory authorities, the Sponsor or Sponsor's designee (Medical Monitor/Expert) will be responsible for determining whether an SAE/SADE is expected (anticipated) or unexpected (unanticipated) in this study[38].

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Investigators or designee will record all qualifying events (adverse events and device deficiencies) with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study Visit, the Investigator or designee will inquire about the occurrence of AE/SAEs since the last visit and or last treatment. Only SAEs unresolved at the last study visit will be followed for outcome information until resolution or until assessed as chronic or stable.

8.3.5 ADVERSE EVENT AND DEVICE DEFICIENCY REPORTING

The occurrence of an AE or SAE may come to the attention of study personnel during study Visits and interviews of a study subject presenting for medical care, or upon review by a study Monitor.

All AEs including local and systemic reactions will be captured on the appropriate CRF. Information to be collected includes event description, (and time, for serious events occurring during the study procedure) onset, Investigator's assessment of severity, seriousness, relationship

[38] Per the recommendation in the US FDA "Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection" (§§ III.B and IV), and in agreement with §§ 812.46(b), 812.150(b)(1), and § 8.2.5 of ISO 14155:2011/COR1:2011 and § 9.2.5 of ISO 14155:2020.

to study device/procedure (assessed only by those with the training and authority to make a diagnosis), expectedness, date (and time, for serious events occurring during the study procedure) of resolution/stabilization of the event, where applicable; and any action taken. All AEs occurring while on study must be documented appropriately regardless of relationship. During the study, all AEs will be followed to adequate resolution or stabilization. In case of adverse events that are still unresolved at the final study Visit; refer to § 8.3.4 for guidance on event follow-up.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE (refer to § 8.3.1). However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE. The AE term in the latter case must be the same term entered at baseline for the preexisting condition and must start with "Worsening of…/ Deterioration of… ".

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. If an ongoing AE worsens in its severity or its relationship to the study device or procedure changes, a new AE entry for the event should be entered on the CRF while the preceding event record should be reported as ended on the same date (113). AEs characterized as intermittent require documentation of onset and duration of each episode.

Laboratory safety measurements and variables reporting

The treating site will perform laboratory analyses according to the protocol-defined Visit schedules and determine protocol-defined parameters. A tabulation of the normal ranges for each parameter required will be enclosed with the measurements done. If at any time a subject has laboratory parameters obtained from a different laboratory, the normal ranges for that laboratory must be recorded with the result obtained. At any time during the trial, abnormal laboratory parameters which are clinically relevant (eg, which lead to interruption of trial treatment, or which lead to clinical symptoms or signs requiring therapeutic intervention), whether specifically requested in the protocol or not, must be recorded on the appropriate CRF form. When abnormal laboratory parameters or test results constitute an SAE, a complete SAE report on the SAE Report form must also be provided.

Notification of deaths

All deaths must be reported to the Sponsor, irrespective of whether the death is related to the device and/or procedure or is an unrelated event. If multiple adverse events are considered to be "causes of death", each event must be entered as a separate AE record. Whenever a subject dies and there is no known cause of death, with no AEs to which the death can be attributed (death

certificate indicates no known cause of death), the AE Term must be entered as "Unknown cause of death".

Device deficiencies

Device deficiencies will be reported on the appropriate CRF form.

Device deficiencies that did not lead to an adverse event but could have led to a serious adverse device effect

a. if suitable action had not been taken, or
b. if intervention had not been made, or
c. if circumstances had been less fortunate,

shall be reported as an SAE (please refer to § 8.3.6).

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Investigator's Responsibilities

Collection, recording, and reporting of SAEs/SADEs or device deficiencies that could have led to a SADE by Investigators to the Sponsor, including any unexpected serious adverse events or serious health threats (refer to § 8.4 below), will be done in an expedited manner using the AE/SAE Report form. Any intercurrent illness, medications, and/or conditions must also be recorded using the relevant CRF form, in the normal manner. All AEs defined as serious and any device deficiencies that could have led to a SADE should be reported to the Sponsor by the Investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE[39]. Receipt of SAE reports will be acknowledged by the Sponsor.

Contact details for safety reporting purposes:

Assaf Lifshitz

Email: assaf@brainqtech.com

[39] In agreement with the US FDA "Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies" (December 2012) and the provisions of § 7.2 of the EC Guidance on "Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC and. 93/42/EEC" (MEDDEV 2.7/3 revision 3, May 2015).

Sponsor's Responsibilities

Reporting of serious adverse events by the Sponsor to regulatory authorities[40] will be done in accordance with the standard operating procedures (SOPs) of the Sponsor or designee (eg, contract research organization [CRO]) and the appropriate regulatory requirements[41].

In general, reportable events[42] will be reported at the same time to all regulatory authorities in whose jurisdiction this clinical investigation has commenced.

Data and Safety Monitoring Board (DSMB) be established in the study under the provisions of § 10.1.6. BrainQ Technologies Ltd. will also report all relevant safety information to the DSMB, according to written procedures.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

Adverse events severity of which corresponds to Grade 3 or higher on the CTCAE v.5.0 scale and that have "probable", "possible" or "causal" relationship with the device and/or the procedure, in accordance with the causality of adverse events as presented in Table 4, must be reported to the Sponsor within 24 hours following the awareness by study personnel at a participating site, unless such events meet the definition of a serious adverse event provided in § 8.3.2, in which case their reporting must adhere to the provisions of § 8.3.6 of this protocol.

8.3.9 REPORTING OF PREGNANCY

Any pregnancy within the term of participation of a subject in the study must be reported by Investigator to the Sponsor. The pregnancy should then be followed-up by the Investigator to determine outcome, including spontaneous or voluntary termination, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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[40] These are referred to as National Competent Authorities (NCAs) in the European Union

[41] In the United States, this will be done in accordance with 21 CFR 812 812.150(b)

[42] The part of the serious adverse event definition in § 8.3.2 appearing in italics is introduced in ISO 14155:2020 is absent from the definition available in CHAPTER I Article 2(58) of the MDR. For the purposes of this trial, the definition in this protocol will apply for Investigator reports to the Sponsor. Applicability of the gap between the definitions in this protocol and the aforementioned MDR definition will be assessed for Sponsor reports to National Competent Authorities if and where MDR will apply to this trial.

NOTE: Pregnancy follow-up does not extend the study for each subject and no data will be collected after the specified study duration for each subject.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involving risks to participants or others will include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency, given a) the research procedures that are described in the protocol-related documents, such as the IRB/EC-approved research protocol and informed consent document; and b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

For this study, UPs include[43]:

- ***Unanticipated adverse device effect*** (UADE[44]) – any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- ***Serious health threat*** is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons[45].

[43] Per the recommendation in the US FDA "Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs - Improving Human Subject Protection" (§§ III.B and IV), and in agreement with 21 CFR §§ 812.46(b), 812.150(a)(1), 812.150(b)(1) and § 9.2.5 of ISO 14155:2020.

[44] Refer to 21 CFR 812.3(s). Consistent with the language defining the unanticipated serious adverse device effect (USADE) in § 3.42 of EN ISO 14155:2011/AC:2011 and § 3.51 of ISO 14155:2020.

[45] § 3.46 of ISO 14155:2020

NOTE: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

8.4.2 UNANTICIPATED PROBLEM REPORTING

An Investigator shall submit to the Sponsor and, if required, to the reviewing IRBs/ECs (and, where applicable, regulatory authority) a report of any unanticipated problem occurring during an investigation[46]. The Sponsor will conduct evaluation of unanticipated problems[47] and report the results of such evaluation to regulatory authorities and to all reviewing IRBs/ECs and participating Investigators.

If an UADE presents an unreasonable risk to subjects, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect. The Sponsor will not resume a terminated investigation without IRB/EC and the U.S. FDA approval[48].

The results of Sponsor's evaluation of unanticipated problems will be reported to the U.S. FDA and to all reviewing IRB's and participating Investigators within 10 working days after the Sponsor first receives notice of the effect[49]. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- **Null hypothesis**:

Mean change in mRS score from baseline (post-stroke day 4-21) to the end of study visit (90 ±15 days post-stroke) in the BQ 2.0 group = mean change in the sham group.

[46] Timelines for reporting to the Sponsor are outlined in § 8.3.6. For IRB reporting in the United States, Investigators should follow the timelines delineated in 21 CFR812.150(a)(1).
[47] 21 CFR 812.46 and § 7.4.4 of ISO 14155:2020
[48] 21 CFR 812.46 and § 8.2.1 of ISO 14155:2020
[49] 21 CFR 812.150(b)(1) § 7.4.4 of ISO 14155:2020

- **Alternative hypothesis**:

Mean change in mRS score from baseline (post-stroke day 4-21) to the end of study visit (90 ±15 days post-stroke) in the BQ 2.0 group ≠ mean change in the sham group.

9.2 SAMPLE SIZE DETERMINATION

A sample size is calculated to test the null hypothesis with 80% power at a 5% two-sided level of significance using a two sample-t-test for simplicity, even though the main statistical analysis may employ a statistically more powerful model-based approach. The estimates used for the mean and standard deviation of the changes from baseline to day 90 are taken from the literature as well as company pilot study data. In the pilot study, the mean change in mRS score from baseline to week 9 in the treatment group was -2.5 (SD=0.66) versus -1.3 (SD=0.46) in the sham group. In the literature a difference of 0.06 points on the mRS between treatment groups is considered clinically meaningful (114). As powering the trial to detect this difference would yield infeasibly large sample sizes, sample size projections were based on detecting a difference as low as 40% of the difference seen in the pilot trial = 0.5-point. To detect a 0.5-point difference between the groups with 80% power at a 5% level of significance using a standard deviation of 1 point and 1:1 allocation ratio, the calculated sample size (PROC POWER in SAS V9.4) is 128 participants in total, 64 participants in each arm. Allowing for a 15% dropout, 150 participants should be randomized.

9.3 POPULATIONS FOR ANALYSES

The following analysis sets are defined for this study:

- Intent-To-Treat (ITT) Analysis Set – will consist of all subjects randomized. In accordance with the ITT principle, all subjects randomized will be kept in their originally assigned treatment group.
- Modified ITT Analysis Set (mITT) – will consist of all subjects from ITT analysis set for whom treatment was initiated and will be analyzed as randomized.
- Per-Protocol Analysis Set (PP) – includes all subjects from the mITT analysis set who have no significant protocol deviations (examples of such potential protocol deviations are listed in § 7.2), were treated for a minimum of 20 completed sessions, with data available for the analysis (defined as at least one data point post baseline) and will be analyzed as treated.
- Safety Analysis Set (SAF) - will consist of all subjects where treatment was initiated, with subjects analyzed as treated.

The SAF analysis set will serve as the principal analysis set for the analysis of safety.

The mITT analysis set will serve as the principal analysis set for efficacy assessments (including for secondary endpoints).

Efficacy assessments (including for secondary endpoints) will also be performed on the PP as well as the ITT analysis set as a sensitivity analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary, NC, USA). Statistical analyses and reporting will be performed in compliance with FDA Guidance E6 and E9 and ISO 14155;2020.

Study data will be summarized with descriptive statistics and presented in tables and figures. Continuous variables will be summarized by a mean, standard deviation, minimum, median, and maximum and categorical variables by a count and percentage. For comparison of continuous variables, the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the chi-squared test or Fisher's exact test will be used as appropriate. A Cochran-Armitage trend test may be used when the response is ranked. For comparison of time to event data, the log-rank test will be used. If multiple measurements are taken in a single subject, statistics described below will be appropriately modified to accommodate the within subject correlation.

Detailed methodologies of the statistical analyses of the data collected in this study will be outlined in a trial-specific Statistical Analysis Plan (SAP). Any changes to planned analyses will be described and justified in the SAP. Analyses outlined in the SAP take precedent over those defined in the protocol to the extent there are any conflicts between the two documents.

Significance Levels and Type I Error

The overall significance level for this study is 5% using two-tailed tests, except for the group by site interaction that will be tested at a significance level of 15%.

The hierarchy (stepwise gatekeeper) approach will be adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing.

The primary endpoint will be analyzed first and only if the null hypothesis is rejected at a 5% level of significance or lower then we shall continue to test the secondary endpoints in a hierarchical manner. Nominal p-values will be reported, even if eventually due to the hierarchy the result is not considered statistically significant.

The hierarchical order of analysis of the secondary endpoint family will be:

1. Lead secondary endpoint: FMA-UE (upper limb motor impairment) – change from baseline (4-21 days post-stroke) to 90 days post-stroke.
2. BBT (upper extremity function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke.
3. 10MWT (gait speed) – change from baseline (4-21 days post-stroke) to 90 days post-stroke.
4. SIS Hand Domain (patient-reported hand function) – change from baseline (4-21 days post-stroke) to 90 days post-stroke.
5. SIS-16 (patient-reported physical functional limitation) – change from baseline (4-21 days post-stroke) to 90 days post-stroke.
6. EQ-5D-5L (health-related quality of life) at 90 days post-stroke.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

The primary endpoint, mRS change from baseline (day 4-21 post-stroke) to 90 days post-stroke, will be compared between the treatment groups using repeated measures analysis of covariance (ANCOVA, SAS® MIXED procedure).

The model will include the following fixed effects: treatment group, visit [categorical – midterm follow-up visit (± 4 days from 20th treatment) and Day 90 follow-up visit (day 90 ± 15 days post-stroke)], treatment group by visit interaction with baseline mRS and age entered as covariates. Age will be entered as a continuous variable so that the potential for co-linearity problems will be minimized. Center will be entered as a random effect. The treatment group by site interaction will be evaluated as well, but not as part of the principal statistical evaluation.

The compound symmetry covariance structure will be used. If the model does not converge, then either the unstructured or autoregressive (AR1) (whichever model has the lower Akaike information criterion statistic) covariance matrix structure will be used instead. At this time point (up to 3 months post stroke), we do not expect a high proportion of dropouts, as a placebo effect of the sham treatment is expected and was taken into consideration in the design of the study. Thus, any missing data at this time point can be considered missing at random. Therefore, since likelihood based repeated measures is also an imputation method, for this evaluation no other method of imputation of missing data is considered beyond the model estimates. Nevertheless, should the missing at random assumption prove to be incorrect, a sensitivity analysis using methods for data imputation may be performed, such as last observed value (LOV) of that endpoint (115). The LOV is defined as the last available post baseline visit data up to and including the last treatment visit or termination visit. Additionally, we may consider multiple

imputation using a model incorporating key baseline prognostic features as well as the last post-randomization if deemed necessary.

The principal statistical analysis will be a comparison between the treatment groups, derived from the visit by treatment group interaction term from the model. The adjusted mean change from baseline in mRS scores at the 90 days post-stroke visit will be estimated from the model (LS Means) interaction term for each group as well as for the difference between the adjusted means and presented together with 95% confidence intervals and level of significance.

The null hypothesis will be rejected in favor of the alternative hypothesis and the study deemed successful if the *P* value is <0.05 and the mean change mRS in the BQ 2.0 group is higher than that of the sham group at the 90 days post stroke visit.

A shift analysis of the primary endpoint will be performed as a sensitivity analysis as well.

Handling of Missing Primary Endpoint Data

By the 90 days post-stroke visit, we do not expect a high proportion of dropouts, as a placebo effect of the sham treatment is expected and was taken into consideration in the design of the study by using conservative estimates of the treatment effect.

All subjects with at least 1 post-baseline measurement will be included in the statistical analyses. The primary endpoint will be analyzed using a likelihood based repeated measures model, which can handle data missing at random.

For the mITT set, missing primary outcome data at day 90 will be imputed with multiple imputation using a model incorporating key baseline prognostic features as well as the last post-randomization observed value (LOV) of that endpoint (115). The LOV is defined as the last available post baseline visit data up to and including the last treatment visit or termination visit. The LOCF imputation method will also be used to carry forward the most recent data prior to withdrawal/dropout as a sensitivity analysis.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The hierarchy approach will be adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. The order of the secondary endpoints in specified above in § 9.4.13.

The change from baseline in FMA-UE, BBT, SIS Hand Domain, SIS-16 and 10MWT, and the EQ-5D-5L score at day 90, will be compared between the groups with analysis of variance adjusting for baseline value, if relevant (§ 9.4.2).

9.4.4 SAFETY ANALYSES

Descriptive statistics will be presented per study group for all safety parameters.

The primary safety variable, the cumulative incidence (and 95% CI) of adverse events (AEs) reported throughout the study in each of the study groups, will be presented in tabular format and will include incidence tables by severity and relationship to study device and/or procedure.

Adverse event rates will be compared between the study groups with a Fisher's exact test.

Serious adverse events will be listed and discussed individually.

Treatment tolerability will be presented. The number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of adverse events will be presented.

In addition, listings of all safety measures and device deficiencies will be produced.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline condition related characteristics (such as measurements taken at screening) will be tabulated and compared between the study groups by data type. Continuous variables will be summarized by a mean, standard deviation, minimum, median, and maximum and categorical variables by a count and percentage. The statistical evaluation of baseline characteristics will include all available data from the ITT set.

9.4.6 PLANNED INTERIM ANALYSES

One interim analysis is planned, after 78 evaluable subjects will complete the study.

Planning an interim analysis that permits an increase in the sample size as described below does not additionally inflate the type I error (116-119). In addition, the final analysis is performed using the conventional test as appropriate for the statistical hypothesis.

Depending on the outcome of the interim analysis, the study will either continue to the originally planned sample size, stop for futility or continue with an increased sample size. These decisions will be made based on the conditional power (CP), which is defined as the conditional probability that the result will exceed a critical value at the interim given the observed effect size.

Note that the interim analysis will be conducted on mITT analysis set.

After all the relevant data is entered into the database, and the database is cleaned, a soft lock to the database will be performed. An independent unblinded statistician (not the study statistician) will perform the assessments described. Only the unblinded statistician and members of the DSMB will be exposed to the interim report. The members of the data monitoring team of the Sponsor, if such a team is designated, will be limited to individuals with relevant expertise who are independent from the personnel involved in conducting or managing the trial. Only these members may have access to the unmasked information of the interim analysis. Investigators and Sponsor representatives will only be informed of the recommendation to continue or to discontinue the trial, or to implement other modifications in the trial procedure and design suggested by the DSMB, and based on the interim results. The unblinded statistician who is responsible for conducting the interim analyses should ensure that the unmasked data is not available to any unauthorized person within or outside the company.

Decision Rules

The study will either continue to the originally planned sample size if the result is "favorable", stop for futility if the result is "unfavorable" or an increase will be made to the sample size if the result is "promising". These decisions will be made based on the conditional power (CP), defined as the conditional probability that the result will exceed a critical value at the interim given the observed effect size $\widehat{\delta_1}$= difference between mean change from baseline mRS score for the BQ 2.0 versus sham groups at the interim look.

Notation:

- n1= sample size at interim analysis.
- n2= original sample size calculated based on assumed effect size.

nmax = the highest sample size the company is willing to use, nmax = 292 subjects (344 randomized including an allowance for a 15% dropout), and is based on a potential smaller effect size of ~0.33.

CPmin = is the calculated minimum CP based on the ratios nmax/n2, n1/n2 and the target study power (80%).

The following are the decision rules for the interim analysis which will be performed upon accrual of ~61% (n1/n2) of the originally planned sample size, ie, 78 evaluable subjects. These depend on the zone into which CP falls at the interim, the calculated CPmin, the maximum sample size designated for the study and the % of the originally planned sample size at which the interim analysis will be performed. Following this principle does not inflate the Type I error.

- If the result is "Unfavorable", ie, CP < CPmin = 32.7375%, ie, interim result is so disappointing that it is not worth increasing the sample size to retrieve conditional power, stop the trial for futility.
- If the result is "Promising", ie, 32.7375% ≤ CP < 80% for the primary endpoint, the sample size is increased to recover the targeted power of 80%. The sample size used will be either the new calculated sample size based on the conditional power (117) or the predetermined maximum sample size of 292 (344 randomized including an allowance for a 15% dropout) subjects, whichever lower.
- If the result is "Favorable", ie, CP ≥ 80% for the primary endpoint, the interim results are sufficiently favorable and the trial continues to the original sample size planned of 128 (150 randomized including an allowance for a 15% dropout) without the need to adaptively increase the sample size.

Controlling the Alpha Level for the Primary Endpoint

The overall alpha level for this study is 5%. Planning an interim analysis that permits an increase in the sample size as described above does not inflate the type I error (116, 118, 119), which means that the testing of the primary endpoint will be at a 5% level of significance.

9.4.7 SUB-GROUP ANALYSES

Subgroup analysis of the primary efficacy endpoint such as demographic or other baseline patient characteristics will be performed. **Potential Sub-groups**

1. Sex
2. Age groups (< 70 vs. ≥ 70 years)
3. Race
4. Ethnicity
5. mRS 3 vs. 4
6. FMA-UE score
7. 10MWT score
8. Received tPA/thrombectomy for the index stroke
9. SAFE score at baseline (<5, 5-7, 8 or more)
10. First stroke or not
11. Right/left sided stroke
12. Stroke mechanism
13. Time from event to first treatment (< 14 days vs. ≥ 15 days)

14. Compliant vs. not-compliant[50]
15. Treatment group assignment guess by the subject (blinding assessment)

Pooling

Subgroup analysis of the primary efficacy endpoint by site will be used to evaluate the poolability of the results. The significance of site-to-site variability in treatment effect will be evaluated by including site to the visit by group interaction term and will be added to the primary model. If the interaction time by site by group is found significant at a 15% level of significance, the reason for this will be further explored and rationalized. This evaluation may include demographic and baseline features, clinical and treatment history, and site comparability in the features found to be associated with the primary efficacy variable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Listings of the efficacy and safety measurements will be provided.

9.4.9 EXPLORATORY ANALYSES

MoCA, ALDS and PHQ-8 scores at 90 days post stroke will be compared between the groups with analysis of variance adjusting for baseline value, if relevant (§ 9.4.2). The change from baseline to day 180 in mRS, SIS Hand Domain and EQ-5D-5L score at day 180, will be compared between the groups with analysis of variance adjusting for baseline value, if relevant. Safety through 180 days will also be summarized. Additionally, Bang's blinding index will be assessed (120).

Health economics data will be collected and analyzed for publication and other scientific purposes, but this is not intended to support regulatory submissions.

Relationship between adherence to treatment as measured by the Qompass and the clinical outcomes will be explored.

9.4.10 ADHERENCE AND RETENTION ANALYSES

The numbers of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (eg,

[50] The compliance analysis will be conducted as an exploratory sensitivity analysis assessing the correlation of number of completed treatments with the primary efficacy endpoint.

lost to follow-up, adverse event, poor compliance). A list of discontinued patients, protocol deviations, and patients excluded from the efficacy analysis will be provided as well. The effects of non-compliance, dropouts, and possible covariates such as age and sex will be assessed to determine the impact on the general applicability of results from this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study device, study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting administration of the study device.

IMPORTANT NOTE: If an Investigator uses the BQ 2.0 without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs[51].

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The informed consent process will comply with 21 CFR Part 50 and the recommendations set out in INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) (§ 4.8 -- Informed Consent of Trial Subjects). A copy of the full guidelines may be found on the ICH website[52]. The U.S. FDA *draft guidance Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors* (July 2014) will be followed.

In obtaining and documenting informed consent, the Investigator will comply with the applicable regulatory requirement(s) and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki, adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly.

Prior to the beginning of the trial, the Investigator must have the IRB (and, where applicable regulatory authority) written approval/favorable opinion of the written informed consent form

[51] 21 CFR 812.150(a)(5)

[52] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

(ICF) and any other written information to be provided to subjects. The Sponsor will supply a proposed ICF, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB and local regulatory authority (if applicable) and a copy of the approved version must be provided to the Sponsor after IRB approval

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

The Investigator, or a person designated by the Investigator, must fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB.

Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, must provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial must be answered to the satisfaction of the subject or the subject's legally acceptable representative. The Investigator or his/her designee should also stress that the subject is completely free to refuse to take part or withdraw from the trial at any time. Prior to a subject’s participation in the trial, the written ICF must be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness must be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to subjects is read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial, and, if capable of doing so, has signed and personally dated the ICF, the witness must sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative.

Prior to participation in the trial, the subject or the subject's legally acceptable representative must receive a copy of the signed and dated written ICF and any other written information provided to the subjects.

During a subject's participation in the trial, the subject or the subject's legally acceptable representative must receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

With the subject's prior consent, the subject's general practitioner may also be informed that they are taking part in the trial. An electronic general practitioner letter template may be provided for this purpose.

The written ICF and any other written information to be provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF, and written information must receive the IRB/EC (and, where applicable regulatory authority) approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative must be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigator(s), Sponsor and regulatory authorities, where applicable. If the study is prematurely terminated or suspended, the Investigator will promptly inform study participants, IRB/EC, and Sponsor, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study Visits schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Determination of possible serious health threat;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements and/or good clinical practice and/or regulatory requirements;
- Data that are not sufficiently complete and/or evaluable;
- Insufficient study enrollment;
- Investigational product supply or manufacturing issues;
- The Sponsor's decision to modify or discontinue product development;
- A request to discontinue the study by a regulatory or health authority.

Study-wide administration of study device will be halted if Grade ≥ 4 AEs determined to have "probable" or "causal" relationship are reported to the Sponsor. The Sponsor will notify the Investigators immediately when the event is reported, and enrollment screens will stop accepting new study participants. Where required, the Sponsor will inform the regulatory authorities of the temporary halt and the disposition of the study.

Similarly, if suspicion of an unacceptable risk, including serious health threat, to subjects arises during the trial, or when so instructed by the IRB/EC or regulatory authorities, the Sponsor shall suspend the clinical investigation while the risk is assessed. The Sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be mitigated is confirmed[53].

DSMB will be established in the study (refer to § 10.1.6 for details), and the Sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible and will provide recommendations for proceeding with the study to the study Sponsor.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/EC and/or regulatory authority(ies).

When a study is prematurely terminated, refer to § 7 for handling of enrolled study participants

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor and its agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence and stored in accordance with the applicable local laws and/or regulations.

In compliance with guidelines regarding the monitoring of clinical studies and in fulfillment of the Investigator's obligation to the Sponsor, it is required that he/she permit the Sponsor's study Monitor and/or applicable regulatory authority representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation (including medical history to verify eligibility, laboratory tests results to verify transcription accuracy, treatment and diagnostic reports, admission/discharge summaries for hospital admissions occurring while the subject is on study and autopsy reports for deaths occurring during or in temporal proximity to the study).

[53] § 7.4.4 and 8.2.1 of ISO 14155:2020

As part of the required content of informed consent, the subjects must be informed that their records will be reviewed by the study Monitors or representatives of regulatory authorities. The subjects will also be informed that representatives of the DSMB may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Should access to the medical record require a separate waiver or authorization, it is the Investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

All information provided to the Investigator by the Sponsor, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator.

The study Monitor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

Throughout this study, the subject data will only be linked to the Sponsor's clinical study database or documentation framework via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, date of birth (to the extent permitted) and/or age, and subject initials (where permitted) may be used to verify the subject and accuracy of the subject's unique identification number. If the subject's name appears on any documents (eg, laboratory analysis report) it must be obliterated before a copy of the document is supplied to the Sponsor for data management or other purposes. Medical information may be provided to the participant's general practitioner or other appropriate medical personnel responsible for the subject's welfare. The subject's contact information will be securely stored at each clinical site for internal use during the study.

Trial findings stored on computer will be stored in accordance with local data protection laws. The Sponsor and any of its designees will maintain the confidentiality of all subject data and will not disclose information by which subjects may be identified to any third party, other than those directly involved in the treatment of the subject's condition. If the results are published, the subject's identity will remain confidential.

At the end of the study, all records will continue to be kept in a secure location for as long a period as detailed in § 10.1.9.2. Subject's research data, collected for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor. This will not

include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique identification number. The study data entry and study management systems used by clinical sites and by the Sponsor's research staff will be secured and password protected.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored either in the computers of the EDC system provider (refer to § 10.1.9.1 for details). In the event that a paper CRF replaces, temporarily or permanently, the electronic version, data collected using paper forms will be stored at the Sponsor's premises. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Sponsor's premises, under the supervision of the Sponsor, for use by other researchers including those outside of the study. Permission to transmit the data to and store it at the Sponsor's premises will be included in the informed consent. When the study is completed, access to study data will be provided through and by the Sponsor.

Collection of biological samples is not planned in this protocol.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

A list of the study Investigators and participating sites will be provided for inclusion in the trial master file and updates to the list will be provided during the trial.

Study Steering Committee (SSC) will be established and the study and will operate in accordance with a trial-specific charter. List of members of the SSC will be provided for inclusion in the trial master file and updates to the list will be provided during the trial. Its non-independent members may include the study Coordinating Investigator and may also include clinical collaborators and other identified collaborators, and the trial co-coordinators. The Sponsor and the study statistician will be allowed to attend the meetings but will have no voting status. Investigators and key trial personnel may be invited to join the SSC as appropriate to ensure representation from a range of centers and professional groups.

Notwithstanding the obligations of the Sponsor and the Coordinating Investigator assigned for this study, the SSC will be responsible for the overall governance of the trial and will meet by teleconference or in-person as required. The Sponsor will be responsible for administration of the study and for updating the SSC and Investigators and for the exchange of information between the Investigators and members of the SSC.

10.1.6 SAFETY OVERSIGHT

DSMB will be established to oversee the safety and efficacy of the trial. This board will be assembled according to GCP. List of members of the DSMB will be provided for inclusion in the trial master file and updates to the list will be provided during the trial.

Data analyses will be supplied, in confidence, to the DSMB, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further subjects. The DSMB will operate in accordance with a trial-specific charter based upon the template created by the Damocles Group (121). Members of the DSMB will be the only individuals who see the confidential, accumulating data from the trial; however, the Sponsor may receive subsets of the report, as seen fit by the DSMB (eg, accrual, compliance, data completeness). The board will meet as frequently as considered necessary, but at least semiannually, either in person or by teleconference.

The DSMB may consider recommending stopping the trial early if:

- the recruitment rate or data quality are unacceptable;
- there are cases of excessive safety concern that compromise subject safety; or
- results of any interim analysis indicate futility.

The DSMB may also recommend continuation beyond the planned number of subjects in the trial if it is felt that further information might be of interest. If this is recommended, it will be submitted as an amendment, for approval of the applicable IRBs prior to implementation.

Following each meeting, the DSMB will report their findings and recommendations to the Sponsor, or the SSC, should the latter be established in the study (see § 10.1.5 for details). No results relating to the trial will be made available to participants until the Sponsor (or the SSC, if established) considers the data sufficiently mature to justify such a course of action.

DSMB may recommend to the Sponsor or the SSC to suspend recruitment in the event of serious or persistent non-compliance and/or very poor recruitment.

10.1.7 CLINICAL MONITORING

Participating sites will be monitored to confirm compliance with the protocol, and the protection of subjects' rights.

The Monitor will assess the source data and the data collected in the CRF to assure collected data integrity and quality, and will execute proper data governance measures to ensure compliance of the study records with the essential principles of data management throughout the study

lifecycle, ie, the data are attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available.

Any major problems identified during monitoring may be reported to the Sponsor and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the study protocol to the local IRB.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

NOTE: audits may also occur after close-out activities have been completed at the site.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

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

Following written SOPs, the Monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (eg, Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)). Data governance measures to ensure compliance of the study records with the essential principles of data management throughout the study lifecycle (ie, the data are attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available) will include review of source documents by the Monitors.

For more details on data collection and management and study data monitoring please refer to §§ 10.1.9 and 10.1.7, respectively.

The investigational device will be used in strict adherence to the IFU provided by the Sponsor and only by trained operators (clinic operators or caregivers) certified by the Sponsor.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Entries must be made in pen, using black or blue ink, to ensure clarity of reproduced copies, and must be legible. Any errors must be crossed out with a single stroke, the correction inserted and the change initialed and dated by the Investigator or his/her designee, to maintain audit trail. If it is not clear why a change has been made, an explanation must be written next to the change. Typing correction fluid must not be used. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Erasing, overwriting, or use of correction fluid or tape on the original are strictly forbidden.

Clinical data (including AEs, concomitant medications) and clinical laboratory data for this study will be recorded using an electronic CRF (eCRF) solution, in accordance with U.S. Code of Federal Regulations; *Electronic Records; Electronic Signatures* (21 CFR Part 11) and EU Annex 11 *Computerised Systems*, to enable clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed and reported. Investigators and their designees will be provided comprehensive training in the eCRF data collection instruments, by the Sponsor, during the Study Initiation Visit and, if required, later in the trial. Investigators must review and electronically sign the completed eCRF for each study participant.

Hardcopies of the study Visit worksheets may be provided for use as source document worksheets for recording data for each participant enrolled in the study.

All copies of the retained original source documents shall be certified[54].

Transcription of data from paper or electronic sources to the eCRF

Data elements can be transcribed into the eCRF from paper or electronic source documents, other than hardcopy of the eCRF serving as source documents worksheet. For these data elements, the electronic or paper documents from which the data elements are transcribed are the source. These data must be retained by the Investigators and made available for inspection by the study Monitors and/or that of regulatory authorities, if requested (eg, an original or certified copy of a laboratory report, instrument printout, progress notes of the Investigator, the study participant's hospital chart(s), nurses' notes, patient/subject questionnaires).

[54] A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified, (ie, by a dated signature or by generation through a validated process), to have the same information including data that describe the context, content, and structure, as the original (§ 3.7 of ISO 14155:2020)

Data to be collected in case of termination or withdrawal

Whenever participation of a subject is terminated, or subject withdraws from the study:

a. all eCRFs, including follow-up, must be completed, regardless of treatment received, up to the point of withdrawal or termination.
b. all data collected up to the point of withdrawal or termination will be maintained in the database and included in subsequent analyses.
c. information obtainable from public records (eg, death) does not require consent. This information may be recorded on the appropriate eCRF.

Responsibilities

The eCRFs must be completed, signed and dated by the Investigator or his/her designee (as delegated on the Study Responsibilities Form/Delegation Log) within the time frame listed below (Table 5). The Investigator will be responsible for the timing, completeness, and accuracy of the subjects' CRF/eCRFs.

Table 5. Summary of CRF/eCRF forms completion time frame

eCRF	**Schedule for CRF/eCRF completion**
Screening visit	Within 1 day of completion.
Study Procedure	Within 5 days of completion.
Study Follow-up	Within 5 days of completion.
Safety events	Refer to §§ 8.3.5 and 8.3.6
Concomitant medications	Within 5 days of completion of relevant investigational product use.
Study Termination	Within 5 days of termination.

Data management will be the responsibility of the Sponsor. The eCRFs will be checked for missing or unusual values (range checks), timing, and for consistency over time, both manually and by integrated database validation checks. The data may also be periodically queried by the trial statistician. If any problems are identified during in-house monitoring, a clarification request specifying the problem will be sent to the site Investigator. this will be done via the EDC system, however, if access to the EDC system is not possible, temporarily or permanently, a data clarification form (DCF) will be sent to the site. The correct data should be written on the DCF and signed by a responsible person at the site (as assigned on the site's Study Responsibilities Form/Delegation Log. All trial data will be entered and stored in the trial database. Queries, whether electronic or paper, must be answered within 15 business days of receipt.

Data recorded in the eCRF should be derived from source documents and be consistent with the data recorded on the source documents or certified copies of the latter, where source documents are not available in the ISF. Any discrepancies between the eCRF and source documents from

which the eCRF was derived should be explained and captured in a progress note and maintained in the participant's official electronic study record. Clinical data will be transcribed directly from the source documents. The authorized person transcribing the data from the source documents is regarded as the data originator.

Data originators

A list of all authorized data originators will be maintained by the CRO (Syntactx-NAMSA) and made available at each clinical site.

Identification of data originators relies on identification (log-on) codes and unique passwords and it is the responsibility of the data originators to maintain the security and integrity of the authorized usernames and passwords.

The CRO (Syntactx-NAMSA)will keep a list of the individuals with authorized access to the eCRF. Only those individuals who have documented training and authorization will have access to the eCRF data and will be assigned their own identification (log-on) codes and passwords.

eCRF data entry

The eCRF will include an audit report to record who entered or generated the data and when it was entered or generated. Changes to the data will not obscure the original entry, and a record who made the change, when, and why will be maintained.

The audit trail of the eCRF data will be readily available in a human readable form and will provide information that will allow reconstruction and evaluation of the clinical investigation. In the event of temporary or permanent substitution of eCRF with its paper counterpart, the audit trail of the latter will be established and maintained as detailed earlier in this section for the audit trail of the source documents.

Only the Investigators and their designees will perform modifications or corrections to the eCRF data.

The eCRF will feature password protection and employ electronic prompts, flags, and data quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate and minimize errors and omissions during data entry. Prompts will alert the data originator to missing data, inconsistencies, inadmissible values (eg, value or date out of range), and to request additional data where appropriate.

No data identifying subjects by name will be entered into the central study database.

When data elements are transcribed from paper sources into the eCRF, the Investigators will also retain the paper sources, or certified copies, for the period defined in § 10.1.9.2, for regulatory review.

eCRF substitution with paper CRF

In the event that a paper CRF replaces, temporarily or permanently, the electronic version, the rules of completion of the source documents detailed above will apply to paper CRF.

The completed original CRFs must be sent to the Sponsor, with a copy held by the Investigator in their ISF. CRFs completion guidelines must be followed when entering data into CRF. All sections are to be completed before returning the CRF to the Sponsor.

Required regulatory documents

It is the responsibility of the Investigator and study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by the Sponsor, IRB and/or regulatory authority, based on the recommendations published in Annex E of the ISO 14155 standard and § 8 of the ICH GCP E6(R2) guideline. Investigator/Institution should maintain a record of the location(s) of their respective essential documents. The storage system (irrespective of the media used) should provide for document identification, version history, search and retrieval. Elements must include, among others:

a. Patient files containing the source documentation and the informed consent.
b. Investigator files, containing device accountability records, or dispensation logs, where applicable, and all related correspondence.
c. Confidential disclosure agreement with the Sponsor.
d. Investigator files, containing all study related correspondence.
e. Protocol with all amendments
f. Copies of all pre-study documentation and all correspondence to and from the IRB and/or regulatory authority and the Sponsor or Sponsor representatives.
g. Up-to-date version of IB, where applicable.
h. Insurance certificate(s).
i. Up to date (within the past two years) curriculum vitae for the Investigators.
j. Signed and dated Investigator and Site agreement.
k. Assurance that the reviewing IRB complies with the regulatory requirements set forth in U.S. Code of Federal Regulations; *Institutional Review Boards* (21 CFR 56) and/or an equivalent local regulation. The required documentation will consist of the name and address of the IRB and a list of its members, including their titles, occupations, and any institutional affiliations.

l. A copy of the formal written notification to the Investigator regarding approval of the protocol by the IRB (and, where applicable, regulatory authority).
m. A copy of the IRB (and, where applicable, regulatory authority) approved ICF and other adjunctive materials (eg, advertising) to be used in the study, including written documentation of IRB approval of these items.

A guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) acceptable for the purposes of this study is available from the European Medicines Agency[55].

10.1.9.2 STUDY RECORDS RETENTION

It is the responsibility of the Investigator to ensure that all essential trial documentation and source records (eg, signed ICFs, ISFs including all approval letters, pharmacy files, device accountability logs, subjects' hospital notes, copies of CRFs, etc.) are kept after the trial has ended. Investigators shall maintain the records during the investigation and for a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date of notice from the Sponsor that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification. These documents should be retained for a longer period, however, if required by local regulations[56].

The Sponsor will notify Investigators when retention of study records is no longer required. No records will be destroyed without the written consent of the Sponsor. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary. Study records that must be retained include CRFs, signed ICFs, correspondence with the IRB, study device dispensing and inventory records, source documents and screening/enrollment logs.

Should the Investigator relocate or retire, the responsibility for maintaining the study records may be transferred to another Investigator. The Sponsor must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records, provided this does not contradict local

[55] Good Clinical Practice Inspectors Working Group (GCP IWG) Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) [06 December 2018 EMA/INS/GCP/856758/2018] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf
[56] For instance, to comply with CHAPTER III(2) of ANNEX XV of the MDR

regulations. If applicable, notice of a transfer shall be given to the U.S. FDA not later than 10 working days after transfer occurs[57].

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in this clinical investigation protocol (CIP), whether intentional or unintentional, or GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff.

Important (or significant, major) protocol deviations[58] are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being[59], such as:

1. Departure from any protocol inclusion, exclusion, or randomization criterion
2. Failure to promptly report a serious or unexpected AE
3. Unsigned informed consent form
4. BQ 2.0 device used outside protocol / IFU requirements (deviations related to Qompass usage will be considered as non-significant)
5. Other ethical or clinical considerations at the discretion of Investigator
6. Enrolment in another interventional study overlapping with the period of participation in this study

As a result of deviations, corrective and preventive actions (CAPA) are to be developed as required. Protocol deviations and site/investigator non-compliance will be closely monitored by the CRO and the sponsor.

The sponsor reserves the right to suspend enrolment until site retraining occurs and site procedures are defined to prevent further violations. The sponsor also reserves the right to close a site from continued study participation should there be evidence of continued protocol non-compliance.

These practices are consistent with

[57] 21 CFR 812.140(e)

[58] Protocol violation and important (significant) protocol deviation are sometimes used interchangeably to refer to a significant departure from protocol requirements. As the word “violation” may also have other meanings in a regulatory context, “violation” will not be used in this protocol in the context of instance(s) of failure to follow the requirements of the clinical investigation protocol.

[59] E3 Implementation Working Group ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1)

- the following chapters of the ICH *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*[60]:
  a. 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
  b. 5.0 Quality Management, sections 5.0.2, 5.0.3, 5.0.4
  c. 5.1 Quality Assurance and Quality Control, section 5.1.1
  d. 5.20 Noncompliance, sections 5.20.1, and 5.20.2.
- the following chapters of EN ISO 14155:2011 (and, in parentheses, ISO 14155:2020):
  a. 9.6 Compliance with the CIP (10.6)
  b. 8.1 Clinical Quality Assurance and Quality Control (9.1; Clinical Quality Management)

Departures from the protocol may be permissible in a medical emergency, to protect the rights, safety and well-being of human subjects, at the discretion of the Investigator or other physician in attendance. In such an emergency, the Investigator should contact the Sponsor as soon as possible, but no later than within 24 hours of the event, to discuss the circumstances of the emergency.

If possible, the Sponsor should be contacted before any deviation from the protocol is implemented. If the requested deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, approval from the FDA, if applicable, (and, where applicable, additional applicable regulatory authorities) and IRB will also be required[61].

If a protocol deviation was conducted by the site without getting a waiver first, the deviation should be recorded by the Monitor and signed by the Investigator. It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations, and the reasons for deviations, must be addressed in study source documents, in the CRF, and must be reported to the Sponsor.

Protocol deviations must be reported to the local IRB per their guidelines. The site Investigator/study staff are responsible for knowing and adhering to their IRB (and, where applicable, regulatory authority) requirements.

[60] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
[61] 21 CFR 812.150(a)(4) and 812.35(a)

10.1.11 PUBLICATION AND DATA SHARING POLICY

In accordance with any national regulations[62], a description of the clinical investigation shall be registered in a publicly accessible database before recruitment of the first subject. When required by the national regulations, the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation[63].

Access to data

Being the Sponsor, BrainQ Technologies Ltd. will have exclusive ownership of the data and results. In cases where co-sponsorship agreement(s) is in force data ownership issues will follow the signed agreements with co-sponsors. Information obtained from this study may be disclosed to corporate partners and/or consultants of the Sponsor.

Communication of the study results

Methods and results of this trial may be submitted for publication in a peer-reviewed journal. A methods paper, an interim results paper and/or a primary results paper may be prepared according to the specific guidelines in the 'EMAGINE' trial publication policy document. Proposals for secondary papers or presentations must be approved as addressable with study data by majority vote of the voting Steering Committee members. The Steering Committee will establish a Writing Group and designate a Chair, selected from among the proposed authors, guided by site productivity in the trial, known expertise of authors, and past author productivity in the use of the EMAGINE dataset. Further details regarding secondary publications are specified in the 'EMAGINE' trial publication policy document. All manuscripts and abstracts to be presented at professional conferences must be reviewed and approved by the Steering Committee (by majority of voting members) prior to submission. In addition to approval by the Committee, BrainQ must review and approve manuscripts at least 30 days in advance of submission, and abstracts at least 7 days before submission. Additionally, posters and slide sets for presentation at national conferences must be submitted to the Chair of the Steering Committee and a BrainQ Steering Committee representative at least 7 days in advance of the presentation for review and approval. Authors must acknowledge that the trial was sponsored by BrainQ Technologies Ltd. Intellectual property rights belong to BrainQ Technologies Ltd.

Authorship eligibility guidelines

[62] eg, 42 CFR Part 11 in the United States.
[63] § 5.4 of ISO 14155:2020.

Publication authorship will be based on the specific guidelines in the 'EMAGINE' trial publication policy document. Site enrollment total will determine whether PIs and any Co-PIs are included as authors, and the order in which they are listed.

Public access to study documents

The study protocol will be made available on a publicly accessible website.

10.1.12 CONFLICT OF INTEREST POLICY

Financial and other competing interests, if any, of Investigator(s) will be disclosed in the ICF. Conflict of interests of study oversight group members (DSMB and/or SSC; if such are established in the study) will be disclosed and managed by the Sponsor.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

ACH	Acute Care Hospital
ADL	Activities of Daily Living
AE	Adverse Event
AHA	American Heart Association
ALDS	Academic Medical Center Linear Disability Scale
ANOVA	Analysis of Variance (will not be expanded)
ARAT	Action Research Arm Test
BBB	Basso, Beattie, and Bresnahan locomotor test
BBT	Box and Block Test
CDISC	Clinical Data Interchange Standards Consortium
CE	Conformité Européene (European Conformity; will not be expanded)
CFR	Code of Federal Regulations (will not be expanded)
CI	Confidence Interval (will not be expanded)
CIMT	Constraint-Induced Mobility Therapy
CMP	Clinical Monitoring Plan
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus Disease (will not be expanded)
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data Clarification Form
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee; or European Commission (if followed by legislation number)
eCRF	electronic Case Report Form
EDC	Electronic Data Collection
EEG	Electroencephalography
ELF	Extremely Low Frequency
EMF	Electromagnetic Field
EN	European Norm (will not be expanded)
EU	European Union (will not be expanded)
EVT	Endovascular Thrombectomy
FA	Fractional Anisotropy
FDA	Food and Drug Administration
FMA-LE	Fugl-Meyer Assessment for Lower Extremity
FMA-UE	Fugl-Meyer Assessment for Upper Extremity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practices
HDE	Humanitarian Device Exemption
HIPAA	Health Insurance Portability and Accountability Act

HRQoL	Health-Related Quality of Life
IADL	Instrumental Activities of Daily Living
ICF	Informed Consent Form
ICU	Intensive Care Unit
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission (will not be expanded)
IFU	Instructions for Use
IRB	Institutional Review Board
IRF	Inpatient Rehabilitation Facility
IRT	Interactive Response Technology
ISF	Investigator Site File
ISO	International Organization for Standardization
ITT	Intention to Treat
IVT	Intravenous Thrombolysis
IWR	Interactive Web-based Response
MDR	Medical Device Regulation
mITT	Modified Intention to Treat
ML	Machine Learning
MoCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
mRT	modified Randomized as Treated
NCI	National Cancer Institute
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NMES	Neuromuscular Electrical Stimulation
OT	Occupational Therapy
PHQ-9	Patient Health Questionnaire-9
PHQ-8	Patient Health Questionnaire-8
PT	Physical Therapy
QC	Quality Control
RCT	Randomized Controlled Trial
RFA-A	Rankin Focused Assessment-Ambulatory
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SD	Standard Deviation (will not be expanded)
SIS	Stroke Impact Scale
SNF	Skilled Nursing Facility
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SSC	Study Steering Committee
SW	Software
tMCAO	temporary Middle Cerebral Artery Occlusion

UADE	Unanticipated Adverse Device Effect
USA or U.S.	United States of America

10.4 PROTOCOL AMENDMENT HISTORY

Revision	Date	Description of Change	Brief Rationale
1	August 1, 2021	Modifications to statistical plan (such as slight increase of sample size and update of the interim analysis plan), as well as addition of a stratification to the randomization scheme and blindness quality assessment and analysis.	Increase of 5% of dropout allowance due to feedback from clinicians. Some of the changes were a result of a sprint discussion with the FDA.
		Allowing randomization and treatments to be conducted in ACH, and an update in the SOA and visits names, accordingly.	Potential subjects might miss the study enrollment window if discharged late from ACH (4-10 days from stroke). The said change will allow to more eligible patients to be randomized within the said window.
		A focused, long-term outcome assessment on the 180th (±15) day after the stroke was added.	This longer follow up will allow a better characterization of the long-term effect of the treatment
		Slight changes to the inclusion and exclusion criteria	Mainly minor changes in order to simplify, reduce redundancy and/or operationalize the criteria.
		Endpoints forms added as appendix to this revision	N/A
2	January 20, 2022	Updating the official title of the study to: EMAGINE Study	EMAGINE is derived from electromagnetic field Ischemic Stroke - Novel Subacute Treatment. We believe that this name well reflects the shared dream and aspiration of many years of all study members to bring new and effective therapies to stroke patients.
		Extend window of recruitment from 4-10 days to 4-14 days	Based on inputs from active sites and pre-screening data, the widening of the window for recruitment is intended to allow for more patients to be enrolled in the study, as well as to allow the sites more time to complete all screening activities. Scientifically,

			this wider window is in line with the window of recruitment which was in established for the pilot study (BQ3).
		Adding a BQ 2.0 key component (Qompass adhesive)	This component was designed to detect the electromagnetic field that the subject is exposed to, to ensure a subject receives the treatment as intended and allow for in depth monitoring and treatment optimization. During the study, the component will only collect data and the data will not be accessible to any blinded personnel or study participants in order to maintain the blind.
		Add an option for urine or blood pregnancy testing and reliance on test result available through medical records	Potential female subjects might miss the study enrollment window due to laboratory processing time. The said change will allow more eligible patients to be randomized.
		Adding footnotes to Schedule of Assessments re Imaging	Adding clarification with respect to imaging time point and the preferred image type.
		Add an exploratory endpoint for the Qompass	To explore the relationship between adherence to treatment as measured by the Qompass and the clinical outcomes
		Reducing the number of initial in person sessions from 7 to 4	Allow for more flexibility
3	June 01, 2022	Extend window of recruitment from 4-14 days to 4-21 days	Based on inputs from active sites and pre-screening data, the widening of the window for recruitment is intended to allow for more patients to be enrolled in the study, as well as to allow the sites more time to complete all screening activities. Scientifically, this wider window is also in line with the window of recruitment which was used in the pilot study (BQ3).
		Change exclusion criteria #3 from "Previous ischemic or	Given that other inclusion and exclusion criteria require the

		hemorrhagic stroke in the 3 months before the index stroke." To "Previous ischemic or hemorrhagic stroke within 2 weeks before the index stroke."	prospective subjects to be medically stable and with a pre-stroke mRS score of 0-1, 2 weeks are hypothesized to be sufficient time. This change will allow more patients to be enrolled into the study.
		Patient recruitment and treatment setting; change from ACH and IRF to ACH, IRF, SNF, outpatient or home setting	Potential subjects may be enlisted and/or treated at each location, as long as they adhere to the overall inclusion-exclusion criteria. This change will allow more patients to be enrolled into the study.
		Change inclusion criteria #3 from "Age 22 to 80 years of age (inclusive)." To "Age 22 to 85 years of age (inclusive)."	Considering the precautions taken via other inclusion and exclusion criteria (e.g., pre-mRS stroke of 0-1, life expectancy of over 12 months, etc.) which sets specific physical and health conditions thresholds on participation in the study, as well as supporting literature and Steering Committee recommendation, the age limit of 85 was decided as a just balance to allow for more patients to be enrolled into the study.
		Removal of the examples provided in exclusion #5 *(eg, hemianopia, diplopia, severe nystagmus, blindness)*	Removing the examples given to avoid confusion when assessing potential subjects.
		Reducing the number of initial in person sessions from 4 to none, and alternatively allow the operators the discretion to decide when are the subjects and caregivers ready to conduct sessions independently	As different subjects and caregivers require different amount of training, the change will allow for more flexibility while keeping the initial rationale in place.
		Correction to the FMA-UE worksheet	Addition of a clarification of subject physical starting position for items 19-22 which was omitted.
		Updates to the publications and data sharing policy	Updates made to further match SPIRIT guidelines

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12 APPENDICES

12.1 APPENDIX 1 – QUESTIONNAIRES AND FUNCTIONAL TEST

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___/___/____

Rating Form
Rankin Focused Assessment - Ambulation (RFA-A)

Name of rater performing assessment: _____

Information for completing this form was obtained from (check all that apply):

[ ] Patient
[ ] Spouse
[ ] Son
[ ] Daughter
[ ] Father
[ ] Mother
[ ] Physical therapist
[ ] Speech therapist
[ ] Medical record
[ ] Other individual, specify role: _____
[ ] Sister
[ ] Brother
[ ] Other relative, specify relationship: _____
[ ] Friend
[ ] Nurse
[ ] Home health aide
[ ] Occupational therapist
[ ] Physician

Please mark (X) in the appropriate box. Please record responses to all questions (unless otherwise indicated in the text). Please see instruction sheets for further information.

5	BEDRIDDEN	
5.1	**Is the person bedridden?** The patient is unable to walk even with another person's assistance. May frequently be incontinent. May require constant care	☐ Yes ☐ No (5)

If yes, explain:

_____
_____
_____
_____
_____

4	ASSISTANCE TO WALK	
4.1	**Is another person's assistance essential for walking?** Requiring another person's assistance means needing another person to be always present when walking, including indoors around house or ward, to provide physical help, verbal instruction, or supervision. (Patients who use physical aids to walk, e.g. stick/cane, walking frame/walker, but do not require another person's help, are NOT rated as requiring assistance to walk).	☐ Yes ☐ No (4)

If yes, explain:

_____
_____
_____
_____
_____

Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___/___/____

3	ASSISTANCE TO LOOK AFTER OWN AFFAIRS	
	Assistance includes physical assistance, or verbal instruction, or supervision by another person. Central issue--Could the patient live alone for 1 week if he/she absolutely had to?	
3.1	**Is assistance ABSOLUTELY essential for preparing a simple meal?** (For example, able to prepare breakfast or a snack)	☐ Yes ☐ No (3)
3.2	**Is assistance ABSOLUTELY essential for basic household chores?** (For example, finding and putting away clothes, clearing up after a meal. Exclude chores that do not need to be done every day, such as using a vacuum cleaner.)	☐ Yes ☐ No (3)
3.3	**Is assistance ABSOLUTELY essential for looking after household expenses?**	☐ Yes ☐ No (3)
3.4	**Is assistance ABSOLUTELY essential for local travel?** (Patients may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.)	☐ Yes ☐ No (3)
3.5	**Is assistance ABSOLUTELY essential for local shopping?** (Local shopping: at least able to buy a single item)	☐ Yes ☐ No (3)

If yes to any of the above, explain:

_____
_____
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Study Number: _____ Subject Initials: __ __ __ Date of Visit: ___/___/____

2. USUAL DUTIES AND ACTIVITIES. The next sets of questions are about how the patient usually spends his/her day.

2.1 Work

2.1	**Has the new stroke substantially reduced (compared to prestroke status) the person's ability to work (or, for a student, study)?** e.g. change from full-time to part-time, change in level of responsibility, or unable to work at all.	☐ Yes ☐ No (2)

If yes, explain:

_____

_____

_____

2.2 Family responsibilities

2.2	**Has the new stroke substantially reduced (compared to prestroke status) the person's ability to look after family at home?**	☐ Yes ☐ No (2)

If yes, explain:

_____

_____

_____

2.3 Social & leisure activities

(Social and leisure activities include hobbies and interests. Includes activities outside the home or at home. Activities outside the home: going to the coffee shop, bar, restaurant, club, church, cinema, visiting friends, going for walks. Activities at home: involving "active" participation including knitting, sewing, painting, games, reading books, home improvements).

2.3	**Has the new stroke reduced (compared to prestroke status) the person's regular free-time activities by more than one half as often?**	☐ Yes ☐ No (2)

If yes, explain:

_____

_____

_____

2.4 Other physical/medical condition

2.4	**Are the patient's work, family, and/or social/leisure activities substantially reduced by a physical/medical condition other than the stroke that led to trial enrollment?**	☐ Yes ☐ No (2)

Provide explanation if 1) answer is yes, but prestroke assessment section 2 answers were all no, or 2) answer is no, but any prestroke assessment 2 section answer was yes:

_____

_____

_____

Study Number: _ _ _ - _ _ _ _ Initials: _ _ _ Date of Visit: ___ / ___ /____

1. SYMPTOMS AS A RESULT OF THE STROKE
(Can be any symptoms or problems reported by the patient).

1.1 SPONTANEOUSLY REPORTED SYMPTOMS

1.1	**Does the patient have any symptoms resulting from the new stroke?**	◻ Yes ◻ No (1)

If yes, record symptoms here:

_____

_____

1.2. SYMPTOM CHECKLIST

1.2.1	**Does the person have difficulty reading or writing as a result of the new stroke?**	◻ Yes ◻ No (1)
1.2.2	**Does the person have difficulty speaking or finding the right word as a result of the new stroke?**	◻ Yes ◻ No (1)
1.2.3	**Does the person have problems with balance or coordination as a result of the new stroke?**	◻ Yes ◻ No (1)
1.2.4	**Does the person have visual problems as a result of stroke?**	◻ Yes ◻ No (1)
1.2.5	**Does the person have numbness (face, arms, legs, hands, feet) as a result of the new stroke?**	◻ Yes ◻ No (1)
1.2.6	**Does the person have weakness or loss of movement (face, arms, legs, hands, feet) as a result of the new stroke?**	◻ Yes ◻ No (1)
1.2.7	**Does the person have difficulty with swallowing as a result of the new stroke?**	◻ Yes ◻ No (1)
1.2.8	**Does the person have any other symptoms related to the new stroke?**	◻ Yes ◻ No (1)

Details supporting any "Yes" checked boxes in Section 1:

_____

_____

_____

Rankin Grade = ☐

Is this Rankin Grade score lower (better) than the prestroke Rankin Grade? ◻ Yes ◻ No

If yes, explain why:

_____

_____

_____

BrainQ

Site Name &Number:
Subject ID:
Date of Assessment:
Visit Type:

FUGL-MEYER ARM MOTOR ASSESSMENT

REMEMBER TO SCORE THE BEST, NOT SIMPLY THE FIRST, PATIENT PERFORMANCE

Proximal

I Reflexes

1. Biceps or finger flexor reflex	☐ 0 [no reflex]	☐ 2 [reflex elicitable]
2. Triceps reflex	☐ 0 [no reflex]	☐ 2 [reflex elicitable]

II Synergistic: Flexor Synergy

Seated patient is instructed to voluntarily bring affected forearm fully supinated to ear of the affected side, elbow fully flexed, shoulder abducted 90°/externally rotated/retracted/elevated.

3. Shoulder girdle retraction	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
4. Shoulder girdle elevation	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
5. Shoulder abduction	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
6. Shoulder external rotation	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
7. Elbow flexion	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
8. Forearm supination	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]

III Synergistic: Extensor Synergy

Starting with full flexor synergy position (passively placed, if necessary), seated patient is instructed to adduct/internally rotate shoulder & extend elbow towards opposite knee, forearm pronated.
Can support elbow to avoid passive movement due to gravity.

9. Shoulder adduction/internal rotation	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
10. Elbow extension	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]
11. Forearm pronation	☐ 0 [not done at all]	☐ 1 [partly done]	☐ 2 [faultless]

IV Movement combining Synergy

Seated patient is instructed to perform 3 separate actions:

BrainQ

Site Name &Number:
Subject ID:
Date of Assessment:
Visit Type:

12. Actively position affected hand on the lumbar spine.

☐ 0 [not done at all] ☐ 1 [actively passes the anterior superior iliac spine] ☐ 2 [faultless]

13. Pure shoulder flexion, 0-90°, elbow fully extended throughout, forearm in midposition between supination/pronation.

☐ 0 [not done at all or at start of motion, shoulder abduction or elbow flexion occurs] ☐ 1 [partly done or shoulder abduction or elbow flexion occurs during motion] ☐ 2 [faultless]

14. Pronation/supination of forearm, elbow actively flexed ≈90°, shoulder at 0°

☐ 0 [not done at all or shoulder & elbow can't achieve proper position] ☐ 1 [any pronation or supination in correct position] ☐ 2 [faultless]

V Movement out of Synergy

Seated patient is instructed to perform 3 separate actions:

15. Abduct shoulder to 90° (pure abduction), elbow fully extended throughout, forearm pronated.

☐ 0 [not done at all or at start of motion, elbow flexion or supination occurs] ☐ 1 [partly done, or elbow flexion or forearm supination occurs during motion] ☐ 2 [faultless]

16. Pure shoulder flexion, 90°-180°, elbow fully extended throughout, forearm midposition between supination/pronation.

☐ 0 [not done at all or at start of motion, shoulder abduction or elbow flexion occurs] ☐ 1 [partly done, or shoulder abduction or elbow flexion occurs during motion] ☐ 2 [faultless]

17. Pronate/supinate forearm, elbow kept fully extended, shoulder kept between 30°- 90° flexion

☐ 0 [not done at all or shoulder & elbow can't get to proper position] ☐ 1 [any pronation or supination in correct position] ☐ 2 [faultless]

VI Normal Reflex Activity

18. If above 3 tests, Questions 15-17, are faultless, evaluate biceps, triceps, and finger flexor deep tendon reflexes as below. Otherwise, do not complete this deep tendon reflex test and record a score of 0.

☐ 0 [≥ 2 deep tendon reflexes are hyperactive, defined as 3- or higher, or item not tested] ☐ 1 [1 deep tendon reflex is hyperactive, defined as 3- or higher] ☐ 2 [all 3 reflexes present, none are hyperactive, defined as 3- or higher]

PROXIMAL SUBSCORE TOTAL _____

BrainQ

Site Name &Number:
Subject ID:
Date of Assessment:
Visit Type:

Wrist/Hand

VII Wrist

Seated patient is instructed to perform the following tasks with shoulder in 0°, elbow 90°, forearm pronated; can assist patient to achieve this position.

19. Dorsiflex wrist

☐ 0 [can't dorsiflex wrist to 15°]
☐ 1 [can dorsiflex but not against resistance, or elbow flexes/forearm supinates during resistance]
☐ 2 [can dorsiflex against slight resistance]

20. Now repeat alternate wrist movement, dorsiflex/volarflex, with fingers somewhat flexed

☐ 0 [no volitional movements]
☐ 1 [active range of motion is less than passive range of motion]
☐ 2 [faultless and smooth]

Seated patient is instructed to perform the following tasks with shoulder slightly flexed/abducted, elbow 0°, forearm pronated; can assist patient to achieve this position

21. Dorsiflex wrist:

☐ 0 [can't dorsiflex wrist to 15°]
☐ 1 [can dorsiflex but not against resistance, or elbow flexes/forearm supinates during resistance]
☐ 2 [can dorsiflex against slight resistance]

22. Now repeat alternate wrist movement, dorsiflex/volarflex, with fingers somewhat flexed

☐ 0 [no volitional movements]
☐ 1 [active range of motion is less than passive range of motion, or elbow flexes during motion]
☐ 2 [faultless and smooth]

Seated patient is instructed to perform the following tasks with shoulder 0°, elbow 0°, forearm pronated; can assist patient to achieve this position

23. Circumduct wrist:

☐ 0 [can't do]
☐ 1 jerky or incomplete circumduction]
☐ 2 [faultless]

BrainQ

Site Name &Number:
Subject ID:
Date of Assessment:
Visit Type:

VIII Hand

Patient is instructed to perform the following tasks with elbow at 90° (support elbow if necessary, but don't support wrist).

24. Flex (all) fingers

☐ 0 [no flexion] ☐ 1 [some but not full active flexion] ☐ 2 [full as compared with unaffected side]

25. Extend all fingers, starting from position of active (passive if necessary) full flexion

☐ 0 [no extension] ☐ 1 [partial or can release active mass flexion grasp] ☐ 2 [full active extension]

26. Grasp while extending metacarpophalangeal joints II-V and flexing proximal and distal interphalangeal joints

☐ 0 [can not reach position] ☐ 1 [weak grasp] ☐ 2 [grasp maintained against great resistance]

27. Grasp 1 sheet of paper with pure thumb adduction (requires full extension of carpometacarpal joint in thumb, as well as of metacarpophalangeal and interphalangeal joints in thumb and index finger)

☐ 0 [can not do this] ☐ 1 [paper kept in place between thumb and 2nd MC, but not against a slight tug] ☐ 2 [paper held well against a tug]

28. Oppose thumb pad against pad of index finger with pencil interposed

☐ 0 [can not do this] ☐ 1 [pencil kept in place between thumb pad and index finger, but not against slight tug] ☐ 2 [pencil held well against a tug]

29. Grasp cylinder-shaped object, e.g., small can, with volar surface of thumb and index finger wrapped around can

☐ 0 [can not do this] ☐ 1 [cylinder/can kept in place between thumb and index finger, but not against slight tug] ☐ 2 [cylinder/can held well against a tug]

BrainQ

Site Name &Number:
Subject ID:
Date of Assessment:
Visit Type:

30. Grasp a tennis ball with all five fingers

☐ 0 [can not do this] ☐ 1 [ball kept in place between all fingers, but not against a slight tug] ☐ 2 [ball held well against a tug]]

WRIST/HAND SUBSCORE TOTAL _____

Coordination and Speed

IX Coordination/Speed

While patient is blind-folded, place tip of index finger from the knee to the nose, 5 times, in as rapid a succession as possible.

31. Tremor:

☐ 0 [marked tremor] ☐ 1 [slight tremor] ☐ 2 [no tremor]

32. Dysmetria:

☐ 0 [pronounced or unsystematic dysmetria] ☐ 1 [slight and systematic dysmetria] ☐ 2 [no dysmetria]

33. Speed:

☐ 0 [affect hand is 6 or more seconds slower than the unaffected hand] ☐ 1 [affected hand is 2-5 seconds slower than the unaffected hand] ☐ 2 [less than 2 seconds difference between the affected and unaffected hand]

COORDINATION/SPEED SUBSCORE TOTAL _____

PROXIMAL SUBSCORE (Q1-18) _____(0-36)
WRIST/HAND SUBSCORE (Q19-30) _____ (0-24)
COORDINATION/SPEED SUBSCORE (Q31-33) ____ (0-6)

TOTAL FM SCORE (Q1-33) _____ (0-66)

Box and Blocks Test

-Open then check the box, place the divider between the box's two compartments

-Position the box lengthwise along the edge of a standard height table such that the box's compartment that has the cubes is on the same side as the subject's unaffected hand.

-Seat the subject in a standard height chair facing the box. The table's edge should be approximately at the height of the subject's umbilicus. The subject should be comfortable. Proper conduct of the B/B test requires that the subject's back continue to be in contact with the chair's back at all times in order to minimize any contribution of spine flexion to the B/B score.

-The examiner sits directly facing the subject in order to view blocks being transported, and to note discrepancies in technique.

-Test the unaffected hand first

-(A) "I want to see how quickly you can pick up one block at a time with your (right/left) hand (point to the hand being tested), carry it to the other side of the box and then drop it. Make sure your fingertips cross the divider (indicate the divider). Watch me while I show you how"

-Examiner transports three cubes over partition.

-(B) "If you pick up two blocks at a time, they will only count as one. If you drop one on the floor or table do not pick it up. Note that if you drop it after you have carried it across, it will still be counted, and if you drop it before carrying across there are plenty more to pick up instead. If you toss the blocks across the divider without your fingers actually crossing the divider, those blocks will not be scored. Before you start, you will have a chance to practice for 15 sec. Do you have any questions? Place your hands on the sides of the box (indicate). When it is time to start, I will say READY and then GO."

-(C) Say READY, wait 3 seconds, then say GO. Subject performs a 15 sec practice. If mistakes are made, correct them.

-"(D) This will be the actual test. The instructions are the same. Work as quickly as you can. READY…(wait 3 sec)…GO."

-(E) After 1 minute STOP.

-(F) Count the number of blocks transported and record. Subtract blocks transported more than one at a time or if the fingertips did not cross over. Return all blocks to one side of the divider.

-Move the box so that all the blocks are on the same side as the next hand to be tested.

-"Now you are to do the same thing with your (left/right) hand.

-REPEAT (A) - (F) with the left/right hand

SCORING BOX

Score for Right Hand	Score for Left Hand	Affected hand was (circle one)
		Right Left

10-Meter Walk Test: Instructions and Scoring Sheet

Description: The 10-Meter Walk Test is a measure of gait speed

Equipment Needed:

- 2 chairs
- digital stopwatch with hundredths of a second resolution
- measuring tape
- bright-colored masking tape
- open hallway or space

Set-Up Of The Course:

- Find a long hallway or other open space that is free from distractions or traffic
- The course should be straight, level, and flat, with no turns or corners
- The total length of the course is 14 meters
- Use bright-colored masking tape to mark four lines on the course at 0, 2, 12 and 14 meters, as per below (do **not** place tape along the dashed line):

Subjects:

- Wear normal supportive foot apparel. If slippers are worn, they must be well-fitting and not floppy
- Wear any orthotics that are normally worn (e.g. AFO etc.)
- Use any assistive device that are normally used for balance and/or stability (e.g. cane or walker)

What Physical Assistance Is Allowed:

- ALLOWED: Physical assistance with ambulation from one person, such as a therapist
- ALLOWED: A therapist may walk aside or behind the subject to provide assistance for safety
- NOT ALLOWED: Physical assistance with ambulation from two or more persons. If this is needed, the subject is considered non-ambulatory, is not tested, and maximum score (300 seconds) is entered
- NOT ALLOWED: The therapist may not advance the subject's leg. If a subject cannot advance his/her own leg, he/she is considered non-ambulatory, is not tested, and maximum score (300 seconds) is entered
- If the patient requires 2 or more persons, or help advancing the leg, do not test gait

S. Cramer vers January 2021

Test Administration:

- Show the subjects the start and stop points
- Seat the subject in the 0-meter chair during instructions
- When ready to begin testing, **the subject starts in a standing position at the 0-meter line**
- Instruct the subject to walk to the 14-meter chair after you give the "Ready and Go" signal
- NOT ALLOWED: Talking during walking. Neither the examiner nor subject should talk during testing
- NOT ALLOWED: Encouragement during walking. **During walking, do not encourage the subject** in anyway.
- Do not mention the tape locations on the floor--only the location of the 14-meter chair
- **At all times, patient safety is number one**. If you cannot test gait safely using above rules, do not score the 10-meter walk test.

Verbal Directives:

- WHEN THE SUBJECT IS SEATED, say: "You are going to walk to the far chair, which is a distance of 10 meters, or just over 30 feet. You should walk at your usual or normal pace. Do you have any questions?" Subjects should not run to achieve a good score, rather, subjects should walk at their usual or normal pace.
- WHEN THE SUBJECT IS STANDING AT THE 0-METER MARK and is ready to start, say: "Remember, you are to walk to the far chair at your usual or normal pace once I say the start command of 'Ready and Go'"
- CONFIRM THE SUBJECT IS READY AND THEN SAY "Ready and Go"

Recording Time: First Trial

- After you say "Ready and Go":
- START THE STOPWATCH the moment that any part of the subject's foot first crosses the 2-meter line
- STOP THE STOPWATCH the moment any part of the subject's foot crosses the 12-meter line
- RECORD THE TIME IN SECONDS (using hundredths of a second resolution). This is the time in seconds that it took for the subject to travel between the 2-meter and the 12-meter lines

Recording the Time: Second Trial

- ALLOW a 2 minute rest in the 14-meter chair before starting the second trial
- **The subject starts in a standing position at the 14-meter line**
- Start the stopwatch the moment that any part the subject's foot crosses the 12-meter line and stop the stopwatch at the moment that any part of the subject's foot crosses the 2-meter line
- Record the time in seconds (at hundredths of a second resolution) it took the subject to

travel from the 12-meter line to the 2-meter line

Recording Outcomes:

- Record values from both trials into the database
- If the subject cannot take even one step, record the time as maximum time (300 seconds)
- If the subject takes longer than 5 minutes (300 seconds) to complete the test, stop testing at 5 minutes and record a time of 300 seconds
- If an attempt cannot be made to evaluate gait velocity testing, then enter a score of 9999 in both boxes for # seconds and record reason for not testing
- Remember, it is critical to **distinguish subjects who are assessed and are very slow or unable to walk** (enter 300 seconds) **from subjects who cannot be tested** (enter 9999)

 # seconds on Trial 1 _____

 # seconds on Trial 2 _____

If an attempt cannot be made to evaluate gait velocity, please provide explanation here:

If an assistive or orthotic device was used, please record the type here:

Stroke Impact Scale

VERSION 3.0

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from **YOUR POINT OF VIEW** how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 1-2 days, how difficult was it to use your hand that was most affected by your stroke to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Could not do at all**
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

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c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

STROKE IMPACT SCALE 16 (SIS-16)

1. Explain to the subject what the questionnaire is about: "Now I am going to ask some questions about how much difficulty you have had while performing some activities in the past 1-2 days"
2. Ask the subject the following questions exactly as they are written. DO NOT CHANGE the script.

In the past 1-2 days, how difficult was it too...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
A. Dress the top part of your body?	5	4	3	2	1
B. Bathe yourself?	5	4	3	2	1
C. Get to the toilet on time?	5	4	3	2	1
D. Control your bladder (not have an accident)?	5	4	3	2	1
E. Control your bowels (not have an accident)?	5	4	3	2	1
F. Stand without losing balance?	5	4	3	2	1
G. Go shopping?	5	4	3	2	1
H. Do heavy household chores (e.g., vacuum, laundry or yard work)	5	4	3	2	1
I. Stay sitting without losing your balance?	5	4	3	2	1
J. Walk without losing your balance?	5	4	3	2	1
K. Move from a bed to a chair?	5	4	3	2	1
L. Walk fast?	5	4	3	2	1
M. Climb one flight of stairs?	5	4	3	2	1
N. Walk one block?	5	4	3	2	1
O. Get in and out of a car?	5	4	3	2	1
P. Carry heavy objects (e.g., bag of groceries) with your affected hand?	5	4	3	2	1

STROKE IMPACT SCALE 16 (SIS-16)

1. Explain to the subject what the questionnaire is about: "Now I am going to ask some questions about how much difficulty you have had while performing some activities in the past 2 weeks"
2. Ask the subject the following questions exactly as they are written. DO NOT CHANGE the script.

In the past 2 weeks, how difficult was it too...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
A. Dress the top part of your body?	5	4	3	2	1
B. Bathe yourself?	5	4	3	2	1
C. Get to the toilet on time?	5	4	3	2	1
D. Control your bladder (not have an accident)?	5	4	3	2	1
E. Control your bowels (not have an accident)?	5	4	3	2	1
F. Stand without losing balance?	5	4	3	2	1
G. Go shopping?	5	4	3	2	1
H. Do heavy household chores (e.g., vacuum, laundry or yard work)	5	4	3	2	1
I. Stay sitting without losing your balance?	5	4	3	2	1
J. Walk without losing your balance?	5	4	3	2	1
K. Move from a bed to a chair?	5	4	3	2	1
L. Walk fast?	5	4	3	2	1
M. Climb one flight of stairs?	5	4	3	2	1
N. Walk one block?	5	4	3	2	1
O. Get in and out of a car?	5	4	3	2	1
P. Carry heavy objects (e.g., bag of groceries) with your affected hand?	5	4	3	2	1

EQ-5D-5L

Health Questionnaire

English version for the USA

VERSION FOR INTERVIEWER ADMINISTRATION

Note to interviewer: although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on page 2 of the questionnaire, the precise wording must be followed.

If the respondent has difficulty regarding which response to choose, or asks for clarification, the interviewer should repeat the question word for word and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

INTRODUCTION

(Note to interviewer: please read the following to the respondent.)

We are trying to find out what you think about your health. I will explain what to do as I go along, but please interrupt me if you do not understand something or if things are not clear to you. There are no right or wrong answers. We are interested only in your personal view.

First, I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY.

Do not choose more than one answer in each group of questions.

(Note to interviewer: first read all five options for each question. Then ask the respondent to choose which one applies to him/herself. Repeat the question and options if necessary. Mark the appropriate box under each heading. You may need to remind the respondent regularly that the timeframe is TODAY.)

EQ-5D DESCRIPTIVE SYSTEM

MOBILITY

First, I would like to ask you about mobility. Would you say that:

1. You have no problems walking? ☐
2. You have slight problems walking? ☐
3. You have moderate problems walking? ☐
4. You have severe problems walking? ☐
5. You are unable to walk? ☐

SELF-CARE

Next, I would like to ask you about self-care. Would you say that:

1. You have no problems washing or dressing yourself? ☐
2. You have slight problems washing or dressing yourself? ☐
3. You have moderate problems washing or dressing yourself? ☐
4. You have severe problems washing or dressing yourself? ☐
5. You are unable to wash or dress yourself? ☐

USUAL ACTIVITIES

Next, I would like to ask you about usual activities, such as work, study, housework, family or leisure activities. Would you say that:

1. You have no problems doing your usual activities? ☐
2. You have slight problems doing your usual activities? ☐
3. You have moderate problems doing your usual activities? ☐
4. You have severe problems doing your usual activities? ☐
5. You are unable to do your usual activities? ☐

PAIN / DISCOMFORT

Next, I would like to ask you about pain or discomfort. Would you say that:

1. You have no pain or discomfort? ☐
2. You have slight pain or discomfort? ☐
3. You have moderate pain or discomfort? ☐
4. You have severe pain or discomfort? ☐
5. You have extreme pain or discomfort? ☐

ANXIETY / DEPRESSION

Finally, I would like to ask you about anxiety or depression. Would you say that:

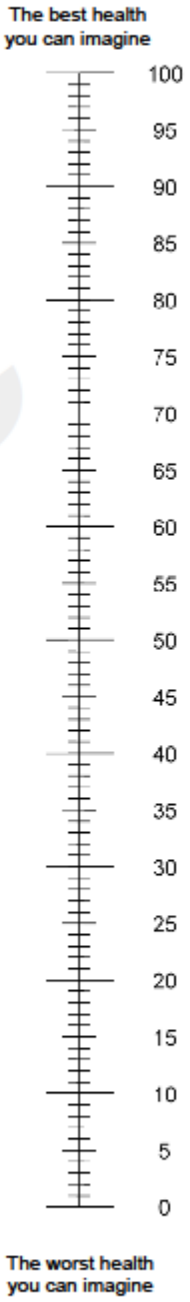
1. You are not anxious or depressed? ☐
2. You are slightly anxious or depressed? ☐
3. You are moderately anxious or depressed? ☐
4. You are severely anxious or depressed? ☐
5. You are extremely anxious or depressed? ☐

EQ-5D VAS

- **Now, I would like to ask you to say how good or bad your health is TODAY.**
- **I would like you to try to picture in your mind a scale that looks like a thermometer.**
  (Note to interviewer: if interviewing face-to-face, please show the person the VAS scale.)
- **The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.**
- **I would now like you to tell me the point on this scale where you would put your health TODAY.**
  (Note to interviewer: mark the scale at the point indicating the respondent's 'health today'. Now, please write the number you marked on the scale in the box below.)

THE RESPONDENT'S HEALTH TODAY = ☐

Thank you for taking the time to answer these questions.

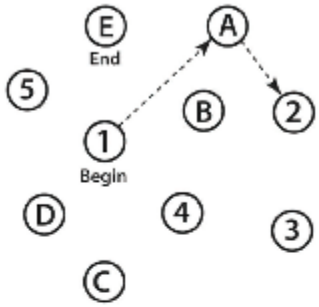


MONTREAL COGNITIVE ASSESSMENT (MOCA®)

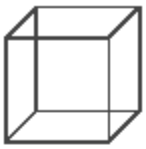
Version 8.1 English

Name:
Education: Date of birth:
Sex: DATE:

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



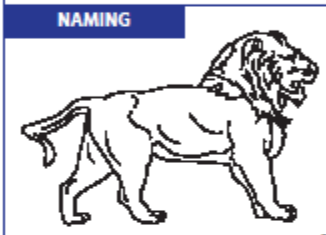
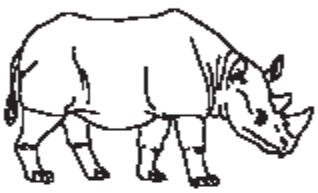
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING


[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1ST TRIAL					
2ND TRIAL					

NO POINTS

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order. [ ] 2 1 8 5 4
Subject has to repeat them in the backward order. [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat: I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F. [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	(MIS)	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
Memory Index Score (MIS)	X3		[ ]	[ ]	[ ]	[ ]	[ ]	
	X2	Category cue						MIS = ____/15
	X1	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Administered by: _____

Training and Certification are required to ensure accuracy

MIS: /15
(Normal ≥ 26/30)
Add 1 point if ≤ 12 yr edu

TOTAL __/30

AMC Linear Disability Score (ALDS)

Introduction

Assessing the clinically meaningful effect on outcome in stroke patients allows more accurate interpretation in clinical trials. The AMC (Academic Medical Center) Linear Disability Score (ALDS) is a calibrated generic item bank to measure the level of physical disability in patients. The ALDS is a sensitive and generic disability scale which measures a broader range of activities compare to the Rankin assessment. The major difference between the ALDS and the Rankin assessment is that the ALDS is a linear disability score assessment and is a patient-reported outcome whereas the Rankin score is an ordinal disability score assessment and is a rater-assigned outcome.

General Instructions

Sources of Information
Obtain information from the same people that provided answers for the Rankin Focused Assessment (RFA).

Choose the Right Assessment
This assessment is intended for use after completing the Rankin Focused Assessment (RFA). There are different sets of questions matched to each Rankin score result. Choose the AMC Linear Disability Score (ALDS) question set according to the Rankin score. For example, if your patient has Rankin score of 3, then assess ALDS 3 question set. However, if every question in the initial ALDS question set ends up marked 'Yes' or 'NA', then please proceed to next lower numbered ALDS question set and complete the assessment *unique* to that ALDS set. For example, if your patient has a Rankin score of 2, then assess ALDS 2. However, if the patient answered all the questions in ALDS 2 'Yes' or 'NA' then proceed to ALDS 1 and assess all the *unique* questions in ALDS 1 that were not in ALDS 2. Similarly, if every question in the initial ALDS question set ends up marked 'No' or 'NA', then please proceed to next higher numbered ALDS question set and complete the assessment *unique* to that ALDS set. For example, if your patient has a Rankin score of 2, then you will complete ALDS 2. If the patient answered all the questions in ALDS 2 'No' or 'NA' then proceed to ALDS 3 and complete all the *unique* questions in ALDS 3.

Rankin Score	Assessment
Rankin Score 0	ALDS 1
Rankin Score 1	ALDS 1
Rankin Score 2	ALDS 2
Rankin Score 3	ALDS 3
Rankin Score 4	ALDS 4
Rankin Score 5	ALDS 5

Scoring Instructions
There are two response options which are 'Yes' and 'No'. If a patient responds that he/she can carry out the activity but only with difficulty, then 'Yes' should be marked. If a patient says the question is not applicable because the patient has never attempted the activity in the question after stroke, then mark the 'NA' box. The answer should reflect what the patient can do without assistance of another person. However, assistance of a walker, cane and other prosthetic devices are fine.

Visit Nurse Name : _____

Patient Number : _____ Subject Initials : __ __ __ Date of Visit : __ / __ / __

AMC Linear Disability Score Rating Form

Information for completing this form was obtained from (please check all that apply) :

◻ Patient	◻ Sister
◻ Spouse	◻ Brother
◻ Son	◻ Other relative, specify relationship : _____
◻ Daughter	◻ Friend
◻ Father	◻ Nurse
◻ Mother	◻ Home health aide
◻ Physical therapist	◻ Occupational therapist
◻ Speech therapist	◻ Physician

◻ Other individual, specify role: _____

Please mark (X) in the appropriate box. Choose the questionnaire according to the Rankin Score. Please assess all the questions. See the instruction sheets for further information.

ALDS 1 : Assessment for Patient with Rankin Score 0 or Rankin Score 1				
		Yes	No	NA
1	Can you vacuum a flight of stairs?	◻	◻	◻
2	Can you carry a bag of shopping upstairs?	◻	◻	◻
3	Can you go for a walk in the woods?	◻	◻	◻
4	Can you travel by local bus?	◻	◻	◻
5	Can you carry a tray?	◻	◻	◻
6	Can you walk up a hill?	◻	◻	◻
7	Can you cut your toe nails?	◻	◻	◻
8	Can you stand for 10 minutes?	◻	◻	◻
9	Can you use a washing machine?	◻	◻	◻
10	Can you walk down a flight of stairs?	◻	◻	◻
11	Can you go for a short walk (15 min)?	◻	◻	◻
12	Can you change the sheets on a bed?	◻	◻	◻
13	Can you buy a few things from the store?	◻	◻	◻
14	Can you take a shower and wash your hair?	◻	◻	◻
15	Can you pick something up from the floor?	◻	◻	◻

Visit Nurse Name : _____

Patient Number : _____ Subject Initials : __ __ __ Date of Visit : __/__/__

Please mark (X) in the appropriate box. Choose the questionnaire according to the Rankin Score. Please assess all the questions. See the instruction sheets for further information.

ALDS 2 : Assessment for Patient with Rankin Score 2				
		Yes	No	NA
1	Can you vacuum a flight of stairs?	☐	☐	☐
2	Can you carry a bag of shopping upstairs?	☐	☐	☐
3	Can you go for a walk in the woods?	☐	☐	☐
4	Can you travel by local bus?	☐	☐	☐
5	Can you carry a tray?	☐	☐	☐
6	Can you go shopping for clothes?	☐	☐	☐
7	Can you cut your toe nails?	☐	☐	☐
8	Can you stand for 10 minutes?	☐	☐	☐
9	Can you use a washing machine?	☐	☐	☐
10	Can you walk down a flight of stairs?	☐	☐	☐
11	Can you change the sheets on a bed?	☐	☐	☐
12	Can you buy a few things from the store?	☐	☐	☐
13	Can you take a shower and wash your hair?	☐	☐	☐
14	Can you pick something up from the floor?	☐	☐	☐
15	Can you prepare breakfast or lunch?	☐	☐	☐

ALDS 3 : Assessment for Patient with Rankin Score 3				
		Yes	No	NA
1	Can you travel by local bus?	☐	☐	☐
2	Can you carry a tray?	☐	☐	☐
3	Can you cut your toe nails?	☐	☐	☐
4	Can you stand for 10 minutes?	☐	☐	☐
5	Can you walk down a flight of stairs?	☐	☐	☐
6	Can you go for a short walk (15 min)?	☐	☐	☐
7	Can you change the sheets on a bed?	☐	☐	☐
8	Can you take a shower and wash your hair?	☐	☐	☐
9	Can you pick something up from the floor?	☐	☐	☐
10	Can you get in and out of a car?	☐	☐	☐
11	Can you prepare breakfast or lunch?	☐	☐	☐
12	Can you put on/take off socks and slippers?	☐	☐	☐
13	Can you sit on the edge of a bed from lying down?	☐	☐	☐
14	Can you put on and take off a coat?	☐	☐	☐
15	Can you walk to and get on and off the toilet?	☐	☐	☐

Visit Nurse Name : _____

Patient Number : _____ Subject Initials : __ __ __ Date of Visit : __ / __ / __

Please mark (X) in the appropriate box. Choose the questionnaire according to the Rankin Score. Please assess all the questions. See the instruction sheets for further information.

ALDS 4 : Assessment for Patient with Rankin Score 4				
		Yes	No	NA
1	Can you carry a tray?	□	□	□
2	Can you walk up a flight of stairs?	□	□	□
3	Can you buy a few things from the store?	□	□	□
4	Can you take a shower and wash your hair?	□	□	□
5	Can you pick something up from the floor?	□	□	□
6	Can you get in and out of a car?	□	□	□
7	Can you peel and core an apple?	□	□	□
8	Can you prepare breakfast or lunch?	□	□	□
9	Can you eat a meal at the table?	□	□	□
10	Can you put on/take off socks and slippers?	□	□	□
11	Can you put pants on?	□	□	□
12	Can you sit on the edge of a bed from lying down?	□	□	□
13	Can you put on and take off a coat?	□	□	□
14	Can you walk to and get on and off the toilet?	□	□	□
15	Can you wash your lower body when taken to sink?	□	□	□

ALDS 5 : Assessment for Patient with Rankin Score 5				
		Yes	No	NA
1	Can you change the sheets on a bed?	□	□	□
2	Can you pick something up from the floor?	□	□	□
3	Can you get in and out of a car?	□	□	□
4	Can you peel and core an apple?	□	□	□
5	Can you eat a meal at the table?	□	□	□
6	Can you put on/take off socks and slippers?	□	□	□
7	Can you sit up (from lying) in bed?	□	□	□
8	Can you get a book off the shelf?	□	□	□
9	Can you answer the telephone?	□	□	□
10	Can you make a bowl of cereal?	□	□	□
11	Can you move between two dining chairs?	□	□	□
12	Can you wash and dry your lower body?	□	□	□
13	Can you put on and take off a coat?	□	□	□
14	Can you wash and dry your face and hands?	□	□	□
15	Can you get out of bed into a chair?	□	□	□

PATIENT HEALTH QUESTIONNAIRE-8 (PHQ-8)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐