GE Healthcare

Study Title: Advanced MRI Applications for Mild Traumatic Brain Injury - Phase 2

Study Number: 114-2015-GES-0017

Revision/Amendment: 4.0

Version Date: 14/Nov/2016

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Investigator's Signature Page

I hereby agree to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, applicable FDA or applicable government regulations, and conditions of approval imposed by the reviewing Ethics Committee, IRB or governing regulatory body;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

Investigator Signature _____ Date _____

Print Name _____

Site Name _____

Site Address _____

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This document contains the following sections:

Document and Version Control

This section records all changes made to the protocol for a specific study. In the table below, record each and every relevant change by indicating what changes were made.

Revision	Date *(DD/Mmm/YYYY)*	Revision Author	Comments/Changes
1.0	01/Jul/2015	Angela Johnson	Clinical writer – Draft finalized based on 28-29/May GE-NFL Medical Advisory Board (MAB) and GEHC internal reviewer comments.
2.0	28/Sep/2015	Angela Johnson	Clinical writer – Revised as per APPENDIX F – AMENDMENT TO PROTOCOL VERSION 1.0 TO 2.0.
3.0	26/May/2016	Angela Johnson	Clinical writer – Revised as per APPENDIX G – AMENDMENT TO PROTOCOL VERSION 2.0 TO 3.0.
4.0	14/Nov/2016	Angela Johnson	Clinical writer – Revised as per APPENDIX H – AMENDMENT TO PROTOCOL VERSION 3.0 TO 4.0.

STUDY SYNOPSIS

Study Title: Advanced MRI Applications for Mild Traumatic Brain Injury - Phase 2
Study Number: 114-2015-GES-0017

Research Type: Clinical (human) ☒ *parallel segments of mTBI patients and non-TBI volunteers aged ≥15 and ≤50 years old at the time of enrollment*

Investigators/ Study Sites:[1] Up to nine (9) sites may be included in this study, as listed in Appendix 1 – Study Site and Investigator List.

Study Sponsor: GE Healthcare (GEHC) *Sponsor Contact*: John Strohmeyer, Senior Clinical Affairs Project Manger	**Address:** 3000 N Grandview Blvd Waukesha, WI 53188 **Telephone:** +1-609-865-7423 **E-mail:** John.Strohmeyer@ge.com
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Brief Description of Study Purpose: This data-driven study is being conducted for hypothesis generation in population of mild traumatic brain injury (mTBI) patients using advanced applications for magnetic resonance imaging (MRI) developed by the Sponsor, GE Healthcare (GEHC), and corresponding clinical neuropsychological assessments. This data is intended for future use in development of specialized MR acquisition, reconstruction, and processing software intended to identify mTBI biomarkers.

Summary of Study Procedures:

Clinical Site Procedures: Two parallel subject segments will be enrolled, including (1) mTBI patients with recent injury in Segment 1 and (2) subjects without recent TBI injury of similar age and demographic characteristics (non-TBI controls in Segment 2). Baseline health information, demographics, and medical history (including prior TBI injury) will be collected for both segments.

Subjects will attend up to four sequential visits relative to injury date (mTBI subjects) or first study scan date (controls): Visit 1 = ≤72 hr, Visit 2 = 7±2 days, Visit 3 = 14±2 days, and Visit 4 = 90±7 days. The mTBI subjects (Segment 1) may start at Visit 1 or Visit 2. Each visit will include a clinical neuropsychological assessment battery and MR scan with *GE Research Pack II* (including research sequences and clinically useful T1, T2, Flair, and reconstructed SWI and DTI) will be evaluated by the site.

Laboratory Procedures: Clinically acquired MR data (DICOM, P-files, and auxiliary files) will be transferred to an imaging laboratory for *GE Research Pack II* reconstruction of clinically useful views using multiband technology and study post-processing. Post-processed data and evaluations (as indicated on a per-module basis by the Sponsor) will be collected.

FOOTNOTES CORRESPONDING TO NUMERALS IN THE TEXT

[1] The University of Michigan Site (originally Site 007) is removed due to non-participation.

Number of Subjects: Data will be collected for two groups (segments) of subjects: (1) mTBI subjects in Segment 1; and (2) non-mTBI controls in Segment 2. The target of the study is to collect at least 210 complete datasets from mTBI patients and at least 105 complete datasets from control subjects. Accounting for all possible reasons, attrition is estimated at 40%. Thus, a maximum of 350 mTBI subjects and 175 non-TBI controls may be enrolled across all sites. While it is expected that sites should enroll approximately equal numbers of subjects, if possible, all sites are encouraged to accrue eligible mTBI subjects as rapidly as possible on an ongoing basis until the maximum number of subjects across all sites is reached. Thus, it is prospectively expected that per-site accrual may vary based on actual enrollment rates.

Additionally, up to 10 volunteers without mTBI injury and not requiring urgent medical care (Segment 0 volunteer subjects) may be enrolled per-site for training and retraining purposes on study devices.

Each site should enroll approximately half as many control subjects as mTBI subjects that complete two consecutive visits and thus provide two consecutive data points (complete either Visits 1 and 2, or Visit 2 and 3), e.g., one control may be enrolled for every two mTBI subjects. A report of mTBI subject enrollment will be generated by the Sponsor or its delegated contract research organization (CRO) and provided to the site on a monthly basis (30±7 days). The report will categorically detail the number of mTBI subjects completing at least 2 visits based on (in order of priority) gender, age, handedness, highest educational level, and MR system used (if more than one system used at the site) as detailed in Section 5.1.1. Enrollment of non-mTBI controls.

Controls are required to attend Visits 1 and 4, but may also attend Visit 2 and 3 when available. Per site, controls should be enrolled in a manner that achieves the same overall ratio within each characteristic category as the mTBI population that has completed two visits to date (per site, all mTBI patients enrolled from study start to date of monthly summary analysis), with the priority detailed in Table 2 of this protocol.

Device/Product GEHC Modality: Magnetic Resonance (MR)

Device/Product Description:

The device under study is the *GE Research Pack II* advanced MRI application suite developed by the Sponsor, GE Healthcare (GEHC), which consists of acquisition software executable on commercially available Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners and software for multiband image reconstruction and post-processing features (volumetry, Kurtosis, RS fMRI, RSI, and, as applicable, further advanced modules) executable on commercially available image processing workstations. *GE Research Pack II* is optimized for use with the investigational 32-channel head coil for 3.0T GE scanners (Nova Medical).

Site-owned Discovery MR750 3.0T and/or MR750w 3.0T scanners with research coils will be used for acquisition, and commercially available VolumeShare 5 Advantage Workstations (AW) will be used for reconstruction and post-processing. Conventional accessory/ancillary devices, such as alternative MR coils, padding, communication, and safety devices may be provided by the site for use in this study (or by the sponsor, if unavailable for use at any investigational site).

Regulatory Status:

Pre-Market	☒	*GE Research Pack II and the 32-channel head coil for 3.0T MR systems (Nova Medical) are investigational medical devices. When used in conjunction with GE Research Pack II, the Discovery MR750 3.0T/MR750w 3.0T MR scanners, conventional coils, VolumeShare 5 Advantage Workstation (AW), and other accessory/ancillary devices used in the study are considered investigational devices.*
Post-Market	☐	

1. PRELIMINARY INVESTIGATIONS AND JUSTIFICATION

1.1. Literature Review

Over 1.1 million traumatic brain injuries (TBI) occur in United States emergency departments annually, including 50,000 fatalities and 43.4% chronic disability. [1] Up to 31.6% of the global population will experience TBI during their lifetime. [1, 2] In particular, mild TBI (mTBI) occurs in about 100-300 of 100,000 hospital-treated TBI cases, though actual occurrence in the general population is expected to be above 600/100,000, though many may fail to seek treatment despite potential long-term effects. [3] Cases of mTBI are particularly common in the military, sports, and among motorcyclists and bicyclists, posing a major public health concern worldwide. [4] Thus improved diagnostic and prognostic methods are necessary.

Historically, mTBI has been treated as an "event" perceived to have little or no lasting effect on central nervous and organ systems. [5] Growing awareness of potential long-term impact of mTBI has based on recent reports of unexpectedly prolonged injury and subsequent identification of cerebral biomarkers and anatomical abnormalities has fostered awareness of mTBI, particularly in professional sports and the military. [6, 7] Currently, TBI injuries are commonly categorized by severity as mild, moderate, or severe based on the length of loss of consciousness (LOC), alteration of consciousness (AOC), or post-traumatic amnesia (PTA). [7] However, optimal and practicable routes for describing the interrelated factors in mTBI that play a role in clinical diagnosis, management, and outcomes of mTBI among the general population remain unclear.

While biomarkers of more severe forms of TBI are often readily apparent, mTBI is extremely heterogeneous and complex and often difficult to detect. [8] Many clinicians and researchers now recognize that minute abnormalities following mTBI can result in potentially serious and adverse chronic conditions, including sleeping abnormalities, cognitive impairments, post-traumatic stress syndrome, increased suicide risk, depression, anxiety, and other neuropsychological effects. [2] Furthermore, patients recovering from mTBI have different cognitive symptoms and white matter injury at different time points relative to injury, potentially indicating compensatory mechanisms or plasticity in response to injury. [9, 10]

Comprehensive characterization of mTBI pathophysiology using modern technologies, such as contemporary advanced magnetic resonance imaging (MRI) systems can provide precise information on brain injury magnitude and location. Unlike computed tomography systems, which are less costly but have limited usefulness in mTBI due to relatively low sensitivity to diffuse brain damage, MRI can detect characteristics of regional brain abnormalities necessary for diagnostic and prognostic decision-making. [8, 11, 12] Using advanced MRI pulse sequence and parameter settings, optimized gradient pulses have the potential to yield critical information about cerebral injury, ranging from volumetric and structural data to specific information on neural tract function and metabolite concentrations. Significant scientific advancements, however, will be required before MRI can provide extensive and reliable data required to diagnose and predict progression of mTBI. This exploratory study is conducted to aid in identifying correlations between mTBI imaging and symptoms that can help to improve advanced MRI applications for brain injury developed by the Sponsor, GE Healthcare.

1.2. Background on Clinical Evaluations for mTBI

The challenge of drawing relationships between cerebral abnormalities observed using MRI and clinical symptoms remains one of the most pressing issues in modern mTBI research. This issue is complicated by the lack of standardization in clinical neuropsychological assessments tools for mTBI and the heterogeneity of injury. Notably, numerous different tools have been developed for assessing concussion immediately following military injury ("blast concussion assessments") and immediately following injury in sports ("sideline concussion assessments"). Different organizations, however, have reached very different conclusions on which tool is optimal, and no universal consensus on the optimal tool has been reached. A comprehensive review by McLeod and Leach [13] (2012) compared self-report concussion scales/checklists from 290 original articles published between 1995 and 2008 identified over 20 tools commonly cited in mTBI literature, and a number of additional commercial tools that are now available. Notably, McLeod and Leach [13] also report that very few of these tools were created in a systematic manner that follows scale development processes and published psychometric properties.

Efforts to standardize tools for clinical diagnosis and management of mTBI include the Military Acute Concussion Evaluation (MACE) and US Department of Defense Instruction (DoDI) 6490.11 [14] and numerous commercially available questionnaires and tests. In research, one of the most widely used standardized tools for mTBI assessment is the National Institutes of Health (NIH) National Institutes of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE), a set of multiple domain assessments for collection of clinical and imaging information from diverse TBI patients. [15] The first set of CDEs was developed in 2010 and was well-suited for hospital-based studies of acute TBI in adults. To broaden the utility of the TBI CDEs, experts were asked to update the recommendations to make them relevant to all ages, injury severity, and phases of recovery. The second version of the TBI CDEs (v.2) were developed in 2012 and were organized based on four major study types of epidemiological research: acute injury, hospitalized patients, studies of the rehabilitation for moderate/severe TBI, and mild TBI/concussion research. Many of the CDEs will overlap across study types, which allows for comparisons and meta-analysis across studies. This consistency also allows for continuity across disease areas, enabling increased efficiency and effectiveness of clinical research studies and clinical treatment, increasing data quality, facilitating data sharing, and helping educate new clinical investigators. [15]

1.3. Pre-Clinical Trials and Previous Clinical (human) Experience

This study design is informed by preliminary results of three prior GEHC sponsored clinical studies conducted under the GE-NFL Head Health Initiative in 2014-2015 (GEHC Sponsored study Nos. 114-2013-GES-0017; 114-2014-GES-0001, and 114-2014-GES-0046; GEHC Internal MWS DOC1461400, DOC1499099, and DOC1564473). Prior trials suggest that MR information derived from diffusion (specifically kurtosis measures), fMRI, arterial spin labeling (ASL), volumetry, and other measures may correlate with cognitive assessments and biomarkers of mTBI severity and progression. In addition, outcomes of the TRACK-TBI Multicenter Initiative sponsored by the National Institute of Neurological Disorders and Stroke (NINDS No. RC2NS069409) and the NCAA-DoD Grand Alliance joint venture sponsored by the Department of Defense (DOD) and National Collegiate Athletic Association (NCAA) support the growing interest and body of knowledge regarding clinical use of mTBI MRI applications. [16, 17]

2. RESEARCH DEVICE

2.1. Identification and Description of Devices

2.1.1. *GE Research Pack II* Advanced MRI Application Suite

GE Research Pack II is an advanced MRI application suite developed by the Sponsor, GE Healthcare (GEHC), consisting of acquisition software executable on Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners. The software enables routine reconstruction of images using multiband technology as well as study-specific post-processing of other types of information not typically found in clinical images. *GE Research Pack II* will include a comprehensive set of post-processing modules (volumetry, Kurtosis, RS fMRI, RSI, and, as applicable, further advanced modules) executable on VolumeShare 5 Advantage Workstations (AW). Acquisition includes pulse sequences and corresponding interface software to define radio frequency (RF), gradient pulses, and associated parameters to optimally shape gradient waveforms when used in conjunction with head coils. Echo time as well as imaging parameters for contrast and other characteristics have been enhanced for optimal results in mTBI based on commercially available MR sequences, including a variety of advanced modules like functional MRI (fMRI), transit time mapping (TT mapping), enhanced arterial spin labeling (eASL), 3D-enhanced T2* weighted angiography (eSWAN), and fluid attenuated inversion recovery (FLAIR), as well as specialized T1 and T2 sequences. To maintain and calibrate systems and for training, routine MR accessories such as MR imaging phantoms, may be used in this study. [18, 19]

2.1.2. 32-channel Multiband MR Brain Coil

The 32-channel multiband MR brain coils are designed to speed up scan time with parallel imaging. *GE Research Pack II* is optimized for the 32-channel MR brain coil for GE 3.0T (Nova Medical, Wilmington, Massachusetts, USA). [20] It has high-sensitivity and ASSET performance, minimal noise, fast acceleration rates, and similar construction as conventional coils. Other commercially available MR coils may be used during this study in cases where the participant cannot be scanned with the research coil, as described in the study procedure.

2.1.3. Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners

Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners are whole-body magnetic resonance scanners indicated for diagnostic imaging, spectroscopic imaging, parametric mapping, and/or spectra, dynamic imaging of body structures/functions, including head and neck. Per site practice, routine accessory/ancillary devices may be used, i.e. padding, hearing protection, communication, and safety devices. DV24 or current software will be used.

2.1.4. VolumeShare 5 Advantage Workstation (AW)

Post-processing is completed on a VolumeShare 5 Advantage Workstation (AW), which supports image display, manipulation, reconstruction, post-processing, and selective recording and is intended to be used to create and review diagnostic evidence related to radiology procedures by trained and licensed physicians and/or qualified clinical/medical personnel.

2.2. Regulatory Status

Discovery MR750 3.0T and/or Discovery MR750w 3.0T scanners, VolumeShare 5 Advantage Workstation (AW), MR phantoms, and conventional MR accessory and ancillary devices used in this study, including conventional MR coils, are commercial devices cleared by the US Food and Drug Administration (FDA). These devices are not indicated specifically for mTBI use and may be used in combination with investigational devices and components as part of this study, and are thus treated as investigational devices for research purposes.

GE Research Pack II, including its acquisition and software (multiband reconstruction and post-processing components), and the 32-channel multi-band MR brain coil for GE 3.0T (Nova Medical) are investigational MRI system components that are not currently cleared by the US FDA.

2.2.1. Device Classification and Rationale

Discovery MR750 3.0T and/or Discovery MR750w 3.0T scanners are considered Class II magnetic resonance diagnostic device per 21 CFR §892.1000. MR Coils are considered to be Class II components of a magnetic resonance diagnostic device, per 21 CFR §892.1000. The VolumeShare 5 workstation is considered to be a Class II Picture archiving and communications system per 21 CFR §892.2050.

2.3. Device Risk Analysis

Eligible subjects will be required to satisfy site MR safety screening requirements and will then undergo MR scanning with the *GE Research Pack II* executed on commercial MR systems using the research 32-channel MR brain coil (or alternative commercial coil, in the event that that head size, medical conditions, deformities, anxiety, or other medical issues prevent use of the research coil). The investigational software and MR coil are optimized for technical performance and have similar safety profiles to those found in routine MRI imaging use in clinical settings. All scanning will be conducted using static field strengths of 3.0T or less. To mitigate risk to levels as low as reasonably practicable (ALARP), the study will employ MR safety methods in accordance with the 2013 ACR Guidance Document on MR Safe Practices (J. Magn. Reson. Imaging 2013;37:501–530).[21] Foreseeable adverse events and device effects are described in Section 10.1. - Foreseeable Adverse Events and Device Effects are not expected to exceed those posed by conventional clinical exams on 3.0T MR systems.

2.3.1. Risk Category/Rationale

The MRI systems with *GE Research Pack II* and research coil under study are considered to be non-significant risk devices per the 21 CFR §812.3 definition, as it:

1) is not intended as an implant;
2) is not purported or represented to be for a use in supporting or sustaining human life;
3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and
4) does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Furthermore, according to the US FDA *Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices Guidance for Industry and FDA Staff*, [22] use of MRI devices in this study does not meet the operating conditions of significant risk for MR studies.

2.4. Device Accountability

2.4.1. Issuance of Devices to Clinical Sites

One or more Discovery MR750 3.0T/Discovery MR750w 3.0T series MR scanners will be provided by the investigational sites. Sites may also provide conventional and commercially available MR accessory/ancillary devices for study use (such as imaging workstations, padding, coils, communication devices, and protective equipment), in accordance with standard site practices. In the event that any site does not have conventional ancillary/accessory devices available as required to complete study procedures, these may be provided by the Sponsor.

The Sponsor will provide, install, and configure *GE Research Pack II* acquisition software on site-provided MR systems. The Sponsor may also provide necessary investigational MR coils, imaging phantoms, and accessory/ancillary devices for study use (such as imaging workstations, padding, coils, communication devices, and protective equipment), if not already available for use at the investigational site. The unique identification information for study devices will be recorded.

2.4.2. Issuance of Devices to Imaging Laboratories

If not already available at laboratories executing *GE Research Pack II* software, the Sponsor may provide VolumeShare 5 Advantage Workstation (AWs) for study use. The unique identification information for study devices will be recorded.

The Sponsor will provide, install, and configure *GE Research Pack II* software on these workstations, and, as deemed necessary by the Sponsor, provide training for the use, quality check, and maintenance of these devices.

2.4.3. Labeling of Research Devices

Research devices will be clearly labeled as investigational devices limited to by Federal (or United States) law to investigational use in accordance with per 21 CFR §812.

2.4.4. Device Disposition

At the end of the study, all components of the *GE Research Pack II* and identifiable subject information will be removed and/or uninstalled from study devices through manual or self-expiry procedures, and Sponsor-provided research devices will be returned to the Sponsor or dispositioned in accordance with applicable laws and regulations.

3. OBJECTIVES OF RESEARCH STUDY

3.1. Study Objectives

3.1.1. Primary Objective

This data-driven study is being conducted for hypothesis generation in population of mTBI patients using advanced applications for magnetic resonance imaging (MRI) being developed by the Sponsor, GE Healthcare (GEHC), and corresponding clinical neuropsychological assessments. Acquired data are intended for future use in development of specialized MR acquisition, reconstruction, and processing software intended to identify biomarkers of mild traumatic brain injury (mTBI).

3.1.2. Safety Objective:

Type, incidence, severity, and relatedness to device of adverse events (AEs) will be recorded during active study participation, from when subject enters the MR scanning area until leaving the scanning area at each visit (not followed between visits).

3.2. Study Endpoints

3.2.1. Primary Endpoint

Per-subject, per-visit collection of data elements from clinical sites (as detailed in Appendix E –Data Collection by Study Visit), including:

1) *GE Research Pack II* MR image data (DICOM, P-files, and auxiliary files)
2) Clinical neuropsychological assessment battery results

3.2.2. Safety Endpoint:

Type, incidence, severity, and relatedness to device of adverse events (AEs)

4. DESIGN OF RESEARCH STUDY

4.1. Research Study Design and Rationale

This is an open-label, non-randomized, prospective, multi-site, parallel group (segment), hypothesis-generating study designed to collect data that will aid in future scientific and engineering exploration of correlations between clinical neuropsychological assessments and *GE Research Pack II* advanced MR imaging in mTBI patients. The results are primarily intended for scientific inquiry and engineering development purposes, and may be used in future regulatory submissions.

Hypothesis-generating studies are designed to provide preliminary data for discovering possible leads worthy of further research study. [23] While hypothesis-testing studies are the gold standard of clinical research, the quality of such studies depends crucially on using informed "building blocks" of hypothesis-generating studies that generate pilot and feasibility data. [24] Hypothesis-generating studies are essential precursors to the development of future hypothesis-testing studies. [24] A

hypothesis-generating study is a widely accepted type of research study commonly performed as the first clinical step in pharmaceutical and medical device programs. [23]

4.2. Type of Research Study

Open-Label	☒	*There is a single study procedure, and both subjects and operators are aware of the procedure (no blinding)*
Blinded	☐	
Double-Blinded	☐	
Single-site	☐	
Multi-site	☒	*This study plans to include up to nine (9) sites*
Randomization Procedure:	☐	
Not randomized*:*	☒	*Consecutive mTBI subjects will be enrolled*
Single arm	☐	
Comparator	☐	
Parallel	☒	*There are two parallel segments (mTBI patients in Segment 1 and non-TBI controls in Segment 2)*
Crossover	☐	
Prospective	☒	*Data is prospectively collected*

4.3. Controls and Minimization of Bias

Consecutive eligible mTBI subjects will be enrolled until the target enrollment is reached in order to minimize selection bias. The control population will be enrolled with characteristics that closely resemble those of the mTBI population, as defined by an analysis of the mTBI population completing two or more visits to-date on a monthly basis. Because the population is intentionally broad in this hypothesis-generating study to encompass a wide cross-section of the general clinical mTBI population, there may be confounders for testing specific correlates, which should be considered in study results.

5. STUDY SUBJECTS

5.1. Number of Subjects

Data will be collected for two groups (segments) of subjects: (1) mTBI subjects in Segment 1 and (2) non-mTBI controls in Segment 2. The target of the study is to collect at least 210 complete datasets from mTBI patients and at least 105 complete datasets from control subjects. Accounting for all possible reasons, attrition is estimated at 40%. Thus, a maximum of 350 mTBI subjects and 175 non-TBI controls may be enrolled.

While it is expected that sites should enroll approximately equal numbers of subjects, if possible, all sites are encouraged to accrue eligible mTBI subjects as rapidly as possible on an ongoing basis until the maximum number of subjects across all sites is reached. Thus, it is prospectively expected that some sites may have differing final accrual.

Table 1 – Enrollment for mTBI subjects and controls

Segment	Description	Total enrollment (all sites, *N*)
Segment 1	**mTBI Patients** are adolescents and adults who recently sustained head injury	350 total
Segment 2	**non-mTBI Subjects** are enrolled as a control population	175 total

Additionally, up to 10 volunteers without mTBI injury and not requiring urgent medical care (Segment 0 volunteer subjects) may be enrolled per-site for training and retraining purposes on the investigational devices.

5.1.1. Enrollment of non-mTBI controls

Enrollment Rate: Each site should enroll approximately half as many control subjects as mTBI subjects, at a rate of approximately one control enrollment for each two mTBI subjects that complete at least two visits (1:2). Though it is prospectively expected that actual enrollment rates may vary, it is the investigator's responsibility to maintain this approximate rate in order to minimize possible bias due to variance in scanner performance ("scanner drift") and other possible confounders.

Population Matching: The study aims to achieve overall matched mTBI and control populations across sites. The overall population will be matched for characteristics identified in order of priority in Table 2. To enable sites to select control subjects that match the overall population, a report of mTBI subject enrollment will be generated by the Sponsor or its delegated contract research organization (CRO) and provided to the site on a rolling monthly basis. The report will categorically detail the number of enrolled mTBI subjects with the following characteristics (Table 2). The clinical site, under the supervision of the Principal Investigator, will be ultimately responsible for ensuring that matched controls are selected according to these criteria.

Case-Control Matching: When possible, investigators are also encouraged to enroll individually matched mTBI and control cases of potential medical interest. Priority should be given, however, to ensuring an appropriate overall population match.

Overall Population Reports:

Table 2 – Population characteristics for enrollment of non-TBI controls (Segment 2) based monthly mTBI accrual by order of priority for matching

Priority	Characteristic	Description/Unit
1	**Gender**	Male, or Female
2	**Age (years)**	≥15 to ≤18, >30 to ≤34, >18 to ≤22, >34 to ≤38, >22 to ≤26, >38 to ≤42, >26 to ≤30, >42 to ≤46, or >46 to ≤50
3	**Handedness** [25]	**Left-handed** (habitual or more skillful use of the left hand for writing and for most manual functions), **Right-handed** (habitual or more skillful use of the right hand for writing and for most manual functions), or **Ambidextrous** (Having equal facility in the use of both hands)
4	**Highest educational level** [26]	1. Some high school (9th to <12th grade), 2. High school graduate (12th diploma), 3. Some college no degree (>12th, no diploma), 4. Associate's degree, 5. Occupational Associate's, 6. Bachelor's degree, 7. Master's degree, 8. Professional degree, or 9. Doctoral degree
5	**MR System used**	Each unique system (if more than one system used at the site)

5.2. Subject Population

The populations under study are mTBI patients (Segment 1) and non-TBI controls (Segment 2). The mTBI patients will be diagnosed mTBI based on site practice and the American Congress of Rehabilitation (ACRM) *Definition of Mild Traumatic Brain Injury* (1993), [27] and the certainty of diagnosis will be recorded. Volunteers for training purposes (Segment 0) and non-TBI controls (Segment 2) will also be enrolled. It is well accepted that while some training can be done using simulations (phantoms), the complexity of *in vivo* human cerebral tissues cannot be fully duplicated without the use of living volunteers. [28] Thus, volunteer subjects will be used for essential activities of training/retraining study staff on clinical functionality.

5.3. Protection of Vulnerable Subjects

Eligible study staff, site employees, students, or fellows may volunteer to participate, in accordance with local EC/IRB policies. Investigators and study staff should ensure that no volunteer is under undue influence or coercion to participate, and the decision to volunteer or not will not affect educational, employment, or staff assignment status.

Adolescent subjects aged 15 but less than 18 may be asked to participate as mTBI patients or controls (Segments 1 and 2). Minor subject may not volunteer for training (Segment 0). This research does not involve greater than minimal risk to children as subjects (45 CFR §46.404 and 21 CFR §50.51). Written parental consent and assent to participate is required for minors, in accordance with 45 CFR §46.408 and applicable IRB policy.

5.4. Inclusion and Exclusion Criteria

5.4.1. Inclusion Criteria by Study Segment

Segment 0 (volunteer) Inclusion	Segment 1 (mTBI patients) Inclusion	Segment 2 (non-mTBI subjects) Inclusion
Subjects included as volunteers for training (Segment 0) will: 1. Be aged ≥18 at the time of enrollment; 2. Be able and willing to provide written informed consent for participation.	*Subjects included as mTBI patients (Segment 1) will:* 1. Be aged ≥15 and ≤50 years old at the time of enrollment; 2. Be diagnosed with mTBI according to the standard diagnostic procedures at the investigational site in a timeframe that meets enrollment criteria for enrollment within 72 hours (Visit 1) or 7±2 days (Visit 3) from injury. 3. Be capable of sufficiently clear communication and language fluency to allow the subject to provide written informed consent, or assent with parental or guardian consent for minors, and to complete study assessments (as per Section 5.3 - Protection of Vulnerable Subjects) for participation in all parts of the study.	*Subjects included as non-mTBI controls (Segment 2) will:* 1. Be aged ≥15 and ≤50 years old at the time of enrollment; 2. Are of similar characteristics as the mTBI population in terms of gender, age, handedness, educational level, and scanner criteria (as per Section 5.1.1 Enrollment of non-mTBI controls) 3. Be capable of sufficiently clear communication and language fluency to allow the subject to provide written informed consent, or assent with parental or guardian consent for minors, and to complete study assessments (as per Section 5.3 - Protection of Vulnerable Subjects), for participation in all parts of the study.

5.4.2. Exclusion Criteria by Study Segment

Segment 0 (volunteer) Exclusion	Segment 1 (mTBI patients) Exclusion	Segment 2 (non-mTBI subjects) Exclusion
Subjects will be excluded that: 1. Are currently enrolled in Segment 1 scanning in this study; 2. Unable (such as due to urgent medical care needs) or unwilling to complete study procedures accurately or have any conflict of interest that	*Subjects will be excluded that have:* 1. Loss of consciousness (LOC) ≥5 minutes; 2. Posttraumatic amnesia lasting ≥24 hr following mTBI; 3. Current or prior (within past 10 years) moderate to severe TBI (GCS <13);	*Subjects will be excluded that have:* 1. Diagnosis of mTBI within the past 6 months; 2. Prior (within past 10 years) moderate to severe TBI (GCS <13); 3. Epilepsy with recurring seizures in past 10 years;

could affect study results, in the opinion of the investigator; 3. Have contraindications to MRI scanning, including: a. Current or suspected pregnancy per site practice; b. Other conditions that may constitute a hazard to the subject during study participation, per investigator; c. Inability to comply with any part of the site's MR safety policy.	4. Diagnosis of mTBI within the past 6 months; 5. Epilepsy with recurring seizures in past 10 years; 6. Drug abuse (except marijuana) in past 10 years (if suspected or self-reported confirm by DAST-10 screening); 7. Alcohol abuse (if suspected or self-reported confirm by AUDIT-C screening); 8. Current primary Axis I or II psychiatric disorders, except for disorders classified as minor and not expected to impact study conduct or integrity (as detailed in Appendix C – Screening Axis I/II Disorders): 9. History of brain mass, neurosurgery, stroke, white matter disease, and/or dementia; 10. Known cognitive dysfunction or structural brain disease/malformation; 11. Structural brain injury on prior neuroimaging findings; 12. Been prescribed antipsychotic/antiepileptic medications (including for current or past head injury); 13. Unable (such as due to urgent medical care needs) or unwilling to complete study procedures accurately or have any conflict of interest that could affect study results, in the opinion of the investigator; 14. Contraindications to MRI scanning, including: a. Current or suspected pregnancy, per site practice; b. Other conditions that may constitute a hazard to the subject during study participation, per investigator;	4. Drug abuse (except marijuana) in past 10 years (if suspected or self-reported confirm by DAST-10 screening); 5. Alcohol abuse (if suspected or self-reported confirm by AUDIT-C screening); 6. Current primary Axis I or II psychiatric disorders, except for disorders classified as minor and not expected to impact study conduct or integrity (as detailed in Appendix C – Screening Axis I/II Disorders): 7. History of brain mass, neurosurgery, stroke, white matter disease, and/or dementia; 8. Known cognitive dysfunction or structural brain disease/malformation; 9. Structural brain injury on prior neuroimaging findings; 10. Been prescribed antipsychotic/antiepileptic medications (including for past head injury); 11. Unable (such as due to urgent medical care needs) or unwilling to complete study procedures accurately or have any conflict of interest that could affect study results, in the opinion of the investigator; 12. Have contraindications to MRI scanning, including: • Current or suspected pregnancy per site practice; • Other conditions that may constitute a hazard to the subject during study participation, per investigator; • Inability to comply with any part of the site's MR safety policy.

	c. Inability to comply with any part of the site's MR safety policy.	

5.5. Concurrent Enrollment

5.5.1. Concurrent Research Activities

Because this study does not involve a therapeutic intervention, subjects in all segments may concurrently participate in other research activities outside of this study that do not involve therapeutic interventions for mTBI or other conditions that could confound study results. If a patient decides to concurrently participate in other research studies with disqualifying interventions, in the opinion of the principal investigator, the subject should be withdrawn.

5.5.2. Concurrent Segment Participation

The mTBI patients in Segment 1 may not concurrently participate in other segments of the study. In the event that any subject initially without mTBI (Segments 0 and 2) experiences an mTBI injury during the course of the study, he/she may be discontinued from the current segment and enrolled into the mTBI segment (Segment 1), provided the subject is otherwise eligible for enrollment in Segment 1 and agrees to participate (including signing the Segment 1 informed consent form).

5.6. Screening Subjects for Enrollment

All subjects will be screened according to the standard screening and recruitment procedures of the investigational site and will complete standard of care MR Safety Screening. The site may employ IRB-approved communications to recruit subjects, so long as such materials have been approved in accordance with applicable laws and regulations as well as local IRB policy. All eligible subjects will provide written informed consent, or assent with parental consent for eligible minors, prior to participation in study procedures.

6. PROCEDURES FOR RESEARCH STUDY

6.1. Quality Procedures

6.1.1. Rationale and Background for Quality Procedures

Minute variations or changes in scanner performance can influence the ability of MRI to produce distinguishable characteristics in the brains of mTBI patients. Contemporary studies indicate that use of multiple MRI scanning devices of similar static field strength are acceptable for pooling and have low variance, supporting the feasibility of pooling multi-site MRI data effectively. [29, 30, 31] It is, however, necessary to collect quantitative performance data from MRI scanners to verify the reproducibility and variance between scanners critical to future analysis of the mTBI data collected in this study. The Sponsor will provide training on proper execution of quality procedures.

6.2. Volunteer (Segment 0) Procedures

6.2.1. Scan Procedures

Volunteer MR scan sessions are expected to last approximately 90 min (no more than 120 minutes) with an optional break after 60 minutes of scanning. Study staff should ensure that volunteers continue to meet the criteria for MR safety at the site immediately prior to MRI scanning. Volunteers will be provided with clothing safe for MRI (such as hospital gowns), hearing protection, and protective devices, per the site's standard of care for MRI scanning. Subjects will be told how to communicate with the operator during scanning, and scanning may be stopped at any time if the subject reports discomfort. Volunteer scans may use any combination of study hardware and software necessary for training/retraining purposes, including *GE Research Pack II* acquisition software and conventional MR sequences on the device, research and conventional MR coils, and/or other MR accessory/ancillary devices.

6.2.2. Participation in Multiple Scan Sessions

Subjects enrolled in Segment 0 may participate in one or more MR scan session during the study if the following criteria are met:

1. Volunteer subjects may be scanned once per 24 hour period
2. Volunteer subjects may be scanned no more than 3 time per calendar week
3. Volunteer subjects must have provided written informed consent using the most current IRB-approved ICF. The subject may be given the opportunity to provide consent using the most recent version prior to participation if a more recent IRB-approved ICF is available at the site.

6.2.3. Scan Data

There is no prospective plan to store MR image data from volunteer scans or to conduct post-processing using this data; however, in the event of technical or safety issues data may be shared with the Sponsor for evaluation as part of this research data. The site will maintain a log of volunteer scans (Appendix A – Segment 0 Volunteer Scan Log). Logs may be disclosed and evaluated by the Sponsor to verify acceptability and training completion, and to determine if the site requires additional training.

6.3. mTBI Subject and non-mTBI Control (Segment 1 and 2) Procedures

6.3.1. Visit Schedule

Each mTBI patient (Segment 1) and non-mTBI control (Segment 2) will attend a series of up to 4 visits (Table 3). Subjects in the mTBI group may enroll and start the study at either Visit 1 or Visit 2 based on date of injury, and non-mTBI control subjects will attend visits on a similar schedule based on date of first study scan. Subjects should attend all study visits, when possible. Controls will be enrolled continuously, as described in Section 5.1.1. Enrollment of non-mTBI controls. When possible, if the site is using more than one MR scanner for study purposes, the same scanner should be used for all visits for a single subject.

Table 3 - Visit schedule for mTBI and non-mTBI control segments

Segment	Description	Visit Schedule			
		Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
Segment 1	**mTBI Subjects** (may be enrolled at either Visit 1 or Visit 2, where first visit is considered baseline)	≤72 hr* from injury **(Baseline)**	Day 7±2* from injury	Day 14±2 from injury	Day 90±7 from injury
		NA	Day 7±2* from injury **(Baseline)**	Day 14±2 from injury	Day 90±7 from injury
Segment 2	**non-mTBI Controls**	**Baseline #**	Day 7±2 from baseline (*optional*)	Day 14±2 from baseline (*optional*)	Day 90±7 # from baseline
Segment 0	**volunteer subjects (training)**	Volunteers may participate one or more scans, if they remain eligible and satisfy Section 6.2.2. Participation in Multiple Scan Sessions			

Note: Day 0 is based on **date of injury** for mTBI patients (Segment 1) or the **day of first study scan (baseline)** for patients without mTBI (Segments 0 and 2). The date of first study scan is considered baseline for all subjects.

* mTBI subjects may be enrolled at either Visit 1 or Visit 2.

Non-mTBI subjects should attend visits 1 and 4, and all 4 visits when possible.

6.3.2. Handling Visit Completion, Missed Visits, and Loss to Follow-up

First Visit (Baseline): All Segment 1 (mTBI subjects) and Segment 2 (non-mTBI controls) are required to complete their initial MRI scan and clinical neurological assessment within 24 hours (in either order), and are required to satisfy complete all parts of the visit within the visit window as defined in Table 2 (with the exception of requests for medical history and other historical information, which may be requested and added to the subject record at any time during the study, as data becomes available to the investigators). Any subject that is not able to complete all parts of the first visit within the visit window should be withdrawn from study once this becomes known. No additional information will be collected after the time of withdrawal, but information collected up until this point may be used and disclosed. Withdrawal due to inability to complete a visit is not considered a deviation if the subject is immediately removed from study (withdrawn) and no additional information is collected.

Subsequent Visits – Missed or Incomplete Visits: For all subsequent visits, subjects may remain on study if a visit is missed or incomplete for any reason, at the investigator's discretion (else the subject may be withdrawn). The site will note the reason for any missed or incomplete visits for subjects that remain on study, and these incomplete data sets will not considered a deviation. It is ultimately the responsibility of the investigator to ensure that data is maximally complete, as incomplete case data may impair scientific integrity of the study.

Subsequent Visits – Missed Visit Window (Table 2): If a subject failed to complete a visit within the visit window, he/she may still be eligible to complete future visits as scheduled (Table 2). Except in exceptional circumstances, study procedures should not be conducted outside of the visit windows (Table 2). Any part of a study visit conducted outside of the protocol visit windows should be reported as a deviation.

Lost to Follow-Up: If a subject is not able to be contacted for scheduled visits (Table 2), the subject will be withdrawn from study and considered lost to follow-up. The site should make reasonable attempts to contact all subjects and document these activities as part of the study source documentation stored in the study file. Subjects lost to follow-up are not considered in deviation of the protocol if documentation of reasonable attempt to contact is maintained by the site and the subject is withdrawal is documented in the study record.

Withdrawal: Withdrawals should be documented as per Section 6.5. -Withdrawal and Discontinuation Criteria. Once a subject is withdrawn, he/she is no longer eligible to participate in any future study visits or procedures, but the data collected up until the time of withdrawal may still be used and disclosed as part of this research.

6.3.3. Baseline Data Collection

After the subject is determined eligible according to the inclusion/exclusion and has provided informed consent (and assent for minors), the following will be recorded for each subject:

- **General Medical History and Demographic Information**
- **Prior mTBI Information**: Current (*for mTBI subjects*) or prior TBI information (*for all control and mTBI subjects*), if available for the subject (it is prospectively expected that not all data may be available for each subject):
    - prior medical records
    - relevant laboratory reports
    - neuroimaging (including CT, MRI, or other scans)
    - baseline neuropsychological or cognitive assessments done for sports or occupational purposes (such as SCAT2/3 for sports players), which may be requested from prior care providers and collected as part of study data.
- **Baseline Clinical Information** about the injury (*must be collected within visit window*):
    - injury presentation information

- health assessments (such as vital signs) collected during the visit
- ***Certainty of Diagnosis*** for mTBI patients in Segment 1 (assessed on a 3-point ordinal scale). Eligible subjects are required to meet diagnostic criteria for mTBI at the site. In addition, a qualified physician or clinical psychologist on the study staff will assess certainty of diagnosis based on:

  1 = **Certain mTBI Diagnosis**: Presents with a combination of physical, behavioral/emotional, and/or cognitive symptoms (not pre-existing) where recent head injury is strongly expected to play the central causal role.

  2 = **Probable mTBI Diagnosis**: Presents with at least one physical, behavioral/emotional, and/or cognitive symptoms (not pre-existing) where recent head injury can be reasonably expected to play a causal role.

  3 = **Possible mTBI Diagnosis**: Presents with at least one physical, behavioral/emotional, and/or cognitive symptoms (not pre-existing) where it is uncertain whether or not recent head injury plays a causal role (as in the case where symptoms assessment is complicated by other conditions or diagnoses pre-existing mTBI, such as mood disorders, physical disability, or other chronic conditions or medication use).

Baseline will be considered the day of the first study scan for all subjects, and *Baseline Data* will be inclusive of information collected or requested based on the first visit (*General Medical and demographic information*, and *prior mTBI information*) and information collected at the first visit (*Baseline Clinical Information*). Only *Baseline Clinical Information* is required to be collected and reported within the visit window. Other information, such as medical history and prior records, may be updated in the subject record as it becomes available to the site.

6.3.4. Visit Procedures (Clinical Neuropsychological Assessment and MR Scan)

Each visit will consist of a Clinical Neuropsychological Assessment of symptoms self-report, cognitive behavioral scales, and physical testing (lasting approximately 60 minutes) and an MR scan session using *GE Research Pack II* acquisition software (lasting approximately 60 minutes). The MR scan should be completed within the interval 24 hours before or after the Clinical Neuropsychological Assessment (within 4 hours, when possible). The example listing of data collection to be performed at each visit is shown in Appendix E – Data Collection by Study Visit.

For MR scanning, study staff should ensure that the subject meets the criteria for MR safety at the site immediately prior to MRI scanning. Subjects will be provided with clothing safe for MRI (such as hospital gowns), hearing protection, and protective devices, per the site's standard of care for MRI scanning. Subjects will be told how to communicate with the operator during scanning, and scanning may be stopped at any time if the subject reports discomfort.

All scans will be completed using 32-channel multiband research coil, except in in cases where the 32-channel multiband research coil cannot be used due to: (1) head size, (2) medical conditions, (3) deformities, (4) anxiety, or (5) other medical issues. Alternatively, any commercially available 32-channel MR coil available at the site may be used, and its applicable identifiers (i.e. make, model, etc.) will be recorded.

6.3.5. MR Acquisition Data (Clinical Site Procedure)

For each scan session, the scan operator or designee will record parameters as described in the MR Data (Appendix E – Data Collection by Study Visit) to a Sponsor provided case report form (CRF). DICOM, P-files, and auxiliary files (collected according to the instructions provided by the Sponsor) will be recorded for each visit. This data will be transferred to the Sponsor or its identified contract research organization (CRO) for execution of the *GE Research Pack II* software.

6.3.6. MR Acquisition Image Reads/Evaluations (Clinical Site Procedure)

One or more site radiologist will read the clinically useful sequences acquired from *GE Research Pack II*. For reading, the clinically useful image set includes both the images produced routinely from the clinical interface (T1, T2, and Flair) and images that require reconstruction by the software due to use of multiband technology.

Readers will assess the entire clinically useful image set (T1, T2, and Flair and reconstructed SWI and DTI) according to the *NINDS CDE Tool: Imaging* with additional Sponsor-provided elements (if necessary) added for research purposes. The reader will determine whether each case is normal or abnormal and complete the Sponsor-provided case report form (CRF) for each case.

Readers are not required to be blinded to clinical care. Readers will have access to reconstructions necessary to review the full clinically useful image set (including conventional reconstructions available from the clinical interface and reconstructions of SWI and DTI produced by the GE Research Pack II software, which are not able to be produced on the clinical interface due to use of the investigational multiband technology). Readers will be blinded to other results of post-processing with *GE Research Pack II*.

6.4. MR Data Post-Processing (Imaging Laboratory Procedure)

Data from Segments 1 and 2 will be transferred to an imaging laboratory (Sponsor or contracted CRO) independent of the clinical care facility for *GE Research Pack II* data post-processing. *GE Research Pack II* acquisition data collected at clinical sites will be screened for quality and loaded onto a workstation for execution of the *GE Research Pack II* post-processing modules. Authorized study staff (such as technician, imaging scientist, and/or radiologist) will record post-processing outcomes as detailed in Appendix D – Detail of Post-Processing Assessment Modules. During the course of the study, the Sponsor may provide technical optimizations to post-processing modules, which will be recorded in the device accountability log. The principal investigator and imaging laboratory will be notified of any optimizations in post-processing technology using the form shown in Appendix D. Clinical sites may be asked to resolve issues of data quality or missing data identified by the processing facility or Sponsor.

6.4.1. Incidental Findings

MR imaging in this study is conducted using investigational MR sequences for research purposes. The investigational research sequences are not intended to provide diagnostic information; however, *GE Research Pack II* also contains components that may be useful as reference for the patient's clinical care (including clinically useful T1, T2, Flair, and reconstructed

SWI and DTI MR data). Patient management should not be based solely on data acquired from research sequences. The other research MR images and related data generated as part of study procedures are not intended for use in patient management decisions or to be stored in patient medical records. In the event that a member of the study staff identifies something possibly abnormal in a research MR image that may be of medical significance, they shall notify the principal investigator. The principal investigator will be responsible for evaluating any such incidental findings and, if necessary according to his/her medical judgment, communicating findings to the patient and/or his or her regular physician, in accordance with IRB policy.

6.5. Withdrawal and Discontinuation Criteria

A subject may withdraw from study at any time, for any reason without consequence. The Investigator may withdraw a subject at any time for any reason, including some clinical conditions concurrent enrollment in another interventional research study that could confound results or pose risks to the patient, or use any medication, stimulant, or illicit substance that could interfere with safe study conduct or integrity of research data, in the opinion of the Principal Investigator. In the event that a subject experiences an additional TBI injury during the study period or sustains other significant injury that could interfere with study participation or outcomes, the subject should be withdrawn when the investigator becomes aware of the change in the subject's medical status. In cases where the investigator is unsure if an injury would disqualify the subject, the case should be confirmed with the Sponsor's medical monitor.

The reasons for withdrawal and discontinuation for any subject shall be recorded, when known. These will be reported to the Sponsor. The EC/IRB should be notified per their notification of subject withdrawal policy. All data collected up until the time of subject withdrawal or discontinuation may be used in study analyses, may be used in any and all subsequent subanalyses determined necessary by the Sponsor, and will be stored by the Sponsor or its authorized representative.

> **Note**: For each subject's first visit, the subject must complete their MR scan and neurological assessment per-protocol (baseline and prior medical history data may be collected at any time after enrollment). Thereafter, subjects that miss a visit or attend a visit outside of the scheduled window should not be withdrawn, and may continue in the study. Missing a visit or visit window, however, will be considered a protocol deviation and reported in accordance with Section 9.1. - Management of Protocol Deviations.

7. TRAINING PLAN

Training plan documents and logs of training attendance will be stored in the Sponsor's clinical history file (CHF).

7.1. Training Plan for Research Device

The Sponsor will provide training on the research device and any device optimizations or versions released during the study. The Investigator may request that additional training be provided to staff by the Sponsor or previously trained study staff during the study. MR imaging phantoms may be used in training and retraining during this study, and phantom training data may be collected and disclosed to the Sponsor as part of this study.

7.1.1. Clinical Site Training on the Research Device

The Sponsor will provide necessary training to study staff operating the *GE Research Pack II* acquisition on site MR scanners, and on the use of research coils. Volunteer subjects (Segment 0) may be scanned during device training at the clinical site under the supervision of a Sponsor representative or for training/retraining by site personnel (with or without a Sponsor representative present).

7.1.2. Imaging Laboratory Training on the Research Device

The Sponsor will provide training necessary for the staff of the imaging laboratory providing quality control, conducting post-processing, and evaluating post-processing results. Training will be provided to the imaging laboratory on how to report technical or quality issues in post-processing.

7.2. Training Plan for Protocol

Protocol training is intended for necessary study staff, which includes any individual that will operate the devices involved with the study, collect clinical data that is part of this study, analyze any data associated with the study, or is in any other way involved with this study.

7.2.1. Clinical Site Training

The Sponsor will provide training on the protocol to the clinical site personnel at the study initiation visit. The Sponsor will also provide training on any subsequent study amendments. The scope of training will include, but not be limited to, the research study protocol, study procedures, monitoring plan, completion and collection of Case Report Forms and other data through site visits and electronic transfers, and communications and/or other media such as web meetings.

7.2.2. Imaging Laboratory Training

The Sponsor will provide training to imaging laboratory prior to the start of post-processing procedures at the facility. Staff at the imaging laboratory conducting post-processing may receive separate training sessions necessary for quality control and execution of post-processing procedures. In the event that any changes to the quality control plan or post-processing technology are made, the Sponsor will also provide training, as necessary to ensure post-processing data integrity and completion.

8. DATA ANALYSIS AND STATISTICS

8.1. Overview

This exploratory hypothesis-generating study is primarily conducted to collect data for subsequent engineering and scientific analyses outside of this study. The report will summarize the subjects enrolled and type of datasets collected. Exploratory data analyses will not be part of the report unless deemed necessary. General statistical methods described in this section and/or other parametric or non-parametric methods, as appropriate for data analysis depending

on the distribution of collected data, will be applied in exploratory analysis. Based on actual data distribution from this exploratory study, data transformation may be performed for data analysis.

Clinical Neuropsychological Assessment will not be part of this study report either, but will be included in the exploratory analysis. Before statistical analysis, outcomes from a particular Clinical Neuropsychological Assessment may be summarized in a clinically meaningful way, such as totaling the score of all or some items in the assessment, determining an overall score or severity, or other methods.

8.2. Statistical Analysis Methods

8.2.1. General Statistical Method

As necessary to support exploratory analyses for scientific and engineering purposes and/or regulatory submission, continuous variables will be summarized with standard descriptive statistics including counts, means, standard deviations, medians, and minimum, maximum. Categorical variables will be summarized with frequencies and percentages.

8.2.2. Interim Analysis

No interim analysis is planned.

8.2.3. Handling of Missing Data

No missing data imputation is planned. For subjects with missing data, outcomes may be interpolated or last observation carry forward methods may be applied in the exploratory analysis.

8.2.4. Pass/Fail Criteria of the Study

There are no statistical pass/fail criteria in this hypothesis-generating study. The study will be considered successful if data collection is sufficient to meet the Sponsor's engineering and scientific goals.

9. DEVIATIONS

9.1. Management of Protocol Deviations

Deviations to the protocol may occur when necessary to protect the life or physical well-being of a subject. Except in an emergency, prior approval by the Sponsor is required for changes in, or planned deviations from this protocol. If these changes affect the scientific soundness or the safety and welfare of the subject, prior EC/IRB approval is also required. Planned Protocol Deviation documentation must be filed in the Site Study Regulatory Binder.

There are two types of unplanned protocol deviations, critical deviations and non-critical deviations. All deviations must be documented and reported, the criticality of the deviation will determine the reporting path.

Critical Deviations: Deviations that significantly affect the safety, efficacy, integrity or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC/IRB per the deviation reporting policy.

If an Investigator uses a device without obtaining informed consent, the Investigator shall consider this a critical deviation and report the event to the Sponsor and the EC/IRB within 5 working days of the occurrence.

Sponsor contact for Critical Protocol Deviations:
John Strohmeyer, Senior Clinical Affairs Project Manager
Phone: +1-609-865-7423
john.strohmeyer@ge.com

Non-Critical Deviations: Protocol deviations that DO NOT significantly affect the safety, efficacy, integrity or conduct of the trial. These deviations must be documented on the Case Report Form Protocol Deviation page and will be reviewed by the study monitor.

10.COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

10.1. Foreseeable Adverse Events and Device Effects

MRI does not use ionizing radiation (high-energy radiation that can potentially cause damage to DNA, such as those found in X-rays and CT scans). MRI of 8.0T or less is widely considered non-significant risk for adults and adolescents, in accordance with the limits defined in the US FDA document Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices (June 20, 2014). The safety profile of 3.0T MR scanning is well characterized, and adverse events are expected to occur at frequencies equivalent or less than conventional MRI using commercially-released scanners (adverse events are expected to occur in less than 1 in 100,000 patients; $P < 10^{-5}$). [21] Foreseeable adverse events of 3.0T MRI scanning of the head in this study may include the following:

- During any MRI scan, the use of strong magnets may cause pacemakers, artificial limbs, and other implanted medical devices that contain metal to malfunction or heat up during the exam. Subjects are screened against site MR safety standards to mitigate these risks.
- During any MRI scan, any loose metal objects may cause damage or injury if it gets pulled toward the magnet. Subjects are screened for ferrous metallic objects before entering the scan area to minimize these risks.
- Dyes from tattoos or tattooed eyeliner can cause skin or eye irritation, and subjects may be asked to remove make-up for this reason.
- Medication patches can cause a skin burn, and subjects may be asked to remove these or other attached medical devices before scanning for this reason.
- The wire leads used to monitor an electrocardiogram (ECG) trace or respiration during a scan must be placed carefully to avoid causing a skin burn, and subjects may be asked to remove these or other attached medical devices before because of this.

- Prolonged exposure to radio waves during the scan could lead to slight warming of the body. Patients will be monitored for signs of discomfort throughout scanning to mitigate these risks.
- Rapidly changing magnetic fields can, under certain conditions, cause nerves close to the skin to become stimulated. This is known as Peripheral Nerve Stimulation (PNS). Patients will be monitored for signs of discomfort throughout scanning to mitigate these risks.
- Transient hearing loss or tinnitus can be caused by acoustic noise levels in excess of 99 dB during MRI scanning. Mandatory hearing protection will be used during scanning to minimize acoustic noise levels.
- Feelings of anxiety triggered by the partially enclosed space within the scanner or noise generated during the exam. Patients will be monitored for signs of discomfort throughout scanning to mitigate these risks.

The occurrence of these risks it mitigated to levels as low as reasonably practicable (ALARP) in accordance with the 2013 ACR Guidance Document on MR Safe Practices (J. Magn. Reson. Imaging 2013;37:501–530), [21] within includes MR safety screening and hearing protection guidelines to minimize acoustic noise levels during scanning.

Because subjects are having a neurological assessment that includes physical and cognitive tests, there are some risks to subjects completing these assessments. These include physical or mental stress, fatigue, minor to moderate injury risk associated with physical tests (such falls or abrasions during balance tests, in rare cases), and confidentiality risks due to disclosure of personal information (e.g. sociodemographics, health, and occupational status information). The risks associated with these tests are not expected to exceed those encountered during routine examinations of head injury.

10.2. Adverse Event Definitions

Adverse Event (AE): As defined by EN ISO 14155-2011: 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.

Serious Adverse Event (SAE): As defined by EN ISO 14155 – 2011: an adverse event that

(a) led to death;
(b) led to a serious deterioration in the health of the subject, that either resulted in:
  (1) a life-threatening illness or injury, or
  (2) a permanent impairment of a body structure or a body function, or
  (3) in-subject or prolonged hospitalization, or
  (4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function;
(c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Anticipated: Any adverse event and/or reaction, the specificity or severity of which is consistent with the IRB approved informed consent, protocol, investigator brochure, or product labeling.

Unanticipated adverse device effect (UADE): As defined by 21 CFR §812.3: means 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.

10.3. Management of Adverse Event Reporting

Any adverse events will be recorded in the subjects study record and the Adverse Event Case Report Form. Subjects will be followed for adverse events and device effects from the time they arrive for each study visit (immediately after providing informed consent for the first visit, and upon arriving to the study area for each subsequent visit, until the subject leaves the study area after each visit). The following information should be obtained:

- Description of Event
- Date of onset and resolution
- Intensity (mild, moderate, severe)
  - **Mild**: Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
  - **Moderate**: Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
  - **Severe**: Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.
- Serious (yes/no)
- Relationship to device (unrelated, possibly related, probably related)
  - **Unrelated**: The adverse event is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product
  - **Possibly related**: The adverse event is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product
  - **Probably related**: There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or there is no other reasonable medical explanation for the event.
- Treatment given and/or action taken (procedure stopped, withdrawn from study, no action)
- Anticipated (yes/no)

Adverse events will be reported to the local EC/IRB per their policy.

10.4. Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting

All SAEs and or UADEs will be documented as above and reported both electronically and in writing to the Sponsor within 72 hours of knowledge of the event. The Investigator shall submit the Adverse Event Case Report Form and GEHC_GQP_10.07.005_F002 Site Notification and Assessment of Serious and Unexpected Adverse Events (GEHC internal document DOC0910335) with redacted supporting documentation to SAE mailbox. If the event resulted in the death of a

subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the local EC/IRB per their policy.

Sponsor contact for SAEs and/or UADEs:
Victor Miranda, MD, Executive, Medical Director
Phone: +1-262-544-3633
Fax: +1 800-888-3983
E-mail: SAE@ge.com

If additional information (i.e. outcome of event, date event resolved, additional treatments) is required to submit a follow-up report, the Investigator shall update the AE CRF and resubmit to the Sponsor. The Investigator shall submit the follow-up SAE and/or UADE report to the local EC/IRB per their policy.

10.5. Management of Device Deficiencies/Complaints

Any deficiencies regarding the operation of the device or software or any malfunctions are to be reported to the Sponsor's Clinical Affairs Project Manager. In the event that these deficiencies constitute a device complaint on a post-market system per the US FDA 21 CFR §820.198 definition, the Sponsor's complain handling procedures will be followed.

Sponsor contact for device complaints:
John Strohmeyer, Senior Clinical Affairs Project Manager
Phone: +1-609-865-7423
E-mail: john.strohmeyer@ge.com

11.EARLY TERMINATION OR SUSPENSION

11.1. Criteria for Early Termination or Suspension

The study may be terminated early if the Sponsor determines that unanticipated adverse event(s) presents an unreasonable risk to subjects or for any other reason as Sponsor determines to be appropriate. Termination shall occur no later than 5 working days after the sponsor makes the determination and no later than 15 working days after Sponsor first received notice of the effect. The Sponsor will promptly notify the Investigators of any determination to terminate the study outside of the protocol timeframe. The Sponsor will provide each Investigator with written guidelines/instructions on termination processes and timelines. The Investigator is responsible for reporting the early termination to their local EC/IRB.

11.2. Withdrawal of EC/IRB Approval

The Investigator is to notify the Sponsor of any withdrawal of EC/IRB approval within 5 working days of such occurrence. If the EC/IRB terminates or suspends its approval of the Study, the Investigator will promptly notify Sponsor and provide a detailed written explanation of the termination or suspension. Upon receipt, the sponsor will provide written guidelines/instructions on subject withdrawal/termination processes and timelines.

12.ETHICS COMMITTEE (EC) AND REGULATORY FILINGS

12.1. Ethics Committee Approval Requirements

This study is to be submitted to the ethic committee (EC) or institutional review board (IRB) at the investigational site for review and approval prior to enrolling subjects. The Investigator is responsible for keeping approval current and maintaining appropriate correspondence and reports. Copies of all EC/IRB applications, approval letters, Informed Consent Forms (ICF), and other correspondence are to be sent to the Sponsor, with originals kept in the Site Study Regulatory Binder.

12.2. Management of Protocol Revisions/Amendments

Protocol revisions and/or amendments shall be approved by the Sponsor, the investigational site, and the Principal Investigator. The investigator will assume responsibility for attaining necessary institutional and EC/IRB approvals for necessary amendments or revisions.

12.3. Informed Consent and Privacy Requirements

Informed consent will be obtained from all subjects prior to participation in the study, per the determination of the EC/IRB.

Informed consent will be documented in the source record of each subject. The Investigator or designee will consent the subject per regulatory guidelines which include the subject has ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in the study; upon agreeing to participate in the study, the subject will sign and date the document, and the person who consented the subject will also sign and date the document.

Minor patients enrolled in Segment 1 and Segment 2 (no minor volunteers may be enrolled in Segment 0) will also be required to provide assent to participate. Segment 1 and Segment 2 subjects will provide informed consent for main study.

For adult volunteers in Segment 0, the subject will provide informed consent to cover all scan sessions conducted after the day the ICF is signed (in accordance with the scan session requirements set forth in Section 6.2 - Volunteer (Segment 0) Procedure. If a new version of the ICF is approved by the IRB during the time that the subject is participating, the subject must be re-consented using the latest version of the ICF prior to any subsequent visits. The subject will be given a copy of the signed ICF and the original will be retained with subject files.

13.DATA AND QUALITY MANAGEMENT

13.1. Management of Data

No clinical data or images are expected to be collected for post-processing or data analysis from subjects that participate in Segment 0 scanning, unless unexpected technical or safety issues are observed (in which case data may be shared with the Sponsor for evaluation as part of this research study). MR image data (DICOM) and P-files may be collected to investigate abnormal device functionality issues or complaints reported during Segment 0, in which case these de-

identified images and associated de-identified image or system data may be stored or provided to the Sponsor for engineering purposes.

Data will be submitted from the investigator to the Sponsor or its authorized representative as described in the Data Management Plan (DMP). The Principal Investigator at each participating site is ultimately responsible for submitting data to the Sponsor and ensuring that all data arrives in a timely manner.

MR images and data as well as clinical assessments will be collected from subjects enrolled in this study. All MR images and image data will be labeled with a subject identification designation (SID) that will not contain any identifiable personal information.

The Sponsor (GE Healthcare) may use de-identified image data, Clinical Neuropsychological Assessment data, and other data collected as part of this study (such as prior baseline TBI data, previous TBI data, and prior neuroimaging results related to TBI injury) and other de-identified clinical data for future technology development, marketing purposes, regulatory submissions, publications, published registries or database of mTBI research, or any other possible use, including public collaborative projects with industry leaders and independent research groups.

The approved Data Management Plan (DMP) will be located in the study's Clinical History File (CHF) maintained by the Sponsor.

13.2. Subject De-identification

Each enrolled subject will be assigned a unique Subject Identification number which is used to de-identify subject data. The Investigator or designee will record subject information and assign a unique subject identification number to each subject. These numbers will be assigned in the order of enrollment, in the numbering sequence provided by the Sponsor.

13.3. Completion of Case Report Forms (CRFs)

Data may be collected using paper CRFs, electronic CRFs, and/or data file transfers. Data from Segment 0 volunteers, Segment 1 mTBI patients, Segment 2 non-TBI controls may be recorded, stored, and housed by different means in accordance with the current Data Management Plan (DMP).

To ensure the quality and integrity of the data, it is the responsibility of the Principal Investigator or designee in a timely manner to complete a data collection via paper CRF and/or electronic means for each subject who is enrolled in this study. GEHC will provide paper CRFs and/or instructions for setup and completion of electronic forms. Paper CRF and electronic data will be completed as information becomes available.

If errors or omissions are found in the course of monitoring, a query will be raised and the site shall make the correction per Good Documentation Practices on the CRFs and/or electronic systems. In the event of an audit or data review once the CRFs or electronic data records have been pulled from the site, a Data Clarification Form (DCF) will be generated and the error, omissions or clarifications will be corrected on these forms.

The Principal Investigator or medically qualified designee will sign and date the indicated places on the CRF or provide appropriate confirmation, such as electronic signatures and/or written

signature confirmation for electronic records. This signature will indicate that a thorough inspection of the data has been made and will thereby certify the contents of paper and/or electronic forms.

13.4. Record Retention at the Site

All records pertaining to the conduct of the study, including Case Report Forms and/or electronic records, Informed Consent Forms, Ethics Committee correspondence, and other study documentation must be retained at the Site for inspection at any time by the GEHC Study Monitor or designee to ensure that study procedures are followed. Elements should include the following:

- Subject Files – containing the completed subject CRFs, (signed/dated) Informed Consent Form(s)
- Regulatory Binder – containing the protocol and amendments, EC/IRB submissions and approvals, (blank) Informed Consent Form(s), Site study logs and sub-contracted site qualifications and contracts.
- Reference Manuals – containing the resource list, responsibilities of the Investigator, Sponsor, adverse event and informed consent guidelines, study aids (training material, device screen shots), and other instructions, if applicable

No physical or electronic records will be destroyed without notification and approval by GE Healthcare.

14.MONITORING PLAN

14.1. Interim Data Reviews

The Sponsor may access data throughout the study for purposes of tracking study progress and conducting pilot data evaluations. Pilot evaluations at each site will be conducted after approximately the first 5 mTBI subject (Segment 1) study scans are completed. These are not required to be unique subjects. Thereafter, the Sponsor may access data at any time during the study.

14.2. Brief Description

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the clinical requirements are met. Monitoring visits will ensure adherence to the protocol, completion of informed consents, IRB review of the study, maintenance of records, primary outcomes review and review of the CRFs and source documentation for accuracy and completeness.

14.3. Reference to Approved Monitoring Plan

The approved monitoring plan will be located in the study's Clinical History File (CHF) maintained by the Sponsor.

15.PUBLICATION POLICY

All publications that use data fully or partially acquired in this study are subject to the terms of the contractual agreement between the Sponsor and Site relevant to this research. The Sponsor retains the rights to use and publish this study data in full or in part and any publications thereof, in accordance with intellectual property laws and applicable regulations.

16.ADDITIONAL STUDY MATERIALS/REFERENCES

16.1. Abbreviations and Terminology

ACRM	American Congress of Rehabilitation
ADC	Apparent diffusion coefficient
ADHD	Attention Deficit Hyperactivity Disorder
ALARP	As low as reasonably practicable
AOC	Alteration of consciousness
AUDIT-C	The Alcohol Use Disorders Identification Test
AW	Advantage workstation (VolumeShare 5)
BESS	Balance Error Scoring System
COWAT	Controlled Oral Word Association Test (subtest of the Multilingual Aphasia Examination)
CPS	Commercial Pulse Sequence
CRO	Contract research organization
DAST-10	Drug Abuse Screening Test (10 items)
dB	Decibels
DICOM	Digital Imaging and Communications in Medicine (imaging file standard)
D-KEFS	Delis-Kaplan Executive Function System
DOD	US Department of Defense
DoDI	US Department of Defense Instruction
eASL	Enhanced arterial spin labeling
eSWAN	3D-enhanced T2* weighted angiography
FFOV	Frequency field of View
FFOV	Frequency Field of View
FLAIR	Fluid attenuated inversion recovery
fMRI	functional MRI
FOV	Field of View
GCS	Glasgow Coma Scale
GCS-E	Glasgow Coma Scale - extended
GE Research Pack II	Name of the advance MRI application software suite consisting of acquisition (pulse sequences and related interface) and post-processing components designed for use with the research coil
GOS-E	Extended Glasgow Outcomes Scale
GSC	Graded symptoms checklist
HSS	Hospital for Special Surgery
HVLT-R	Hopkins Verbal Learning Test – Revised
ICA	Independent Component Analysis
LOC	Loss of consciousness
MACE	Military Acute Concussion Evaluation
MR mTBI Biomarkers	Biomarkers of mTBI clinical neurological symptom and MR image, data, and clinical finding clinical evolution
mTBI	Mild traumatic brain injury

NCAA	National Collegiate Athletic Association
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
PD	Proton Density
PFOV	Phase field of view
PFOV	Phase Field of View
PSI	WAIS-IV/WISC-IV Processing Speed Index
PTA	Post-traumatic amnesia
PVP	Polyvinylpyrrolidone
RF	Radiofrequency
RS	Resting state
SAR	Specific Absorption Rate
SCAT	Sports Concussion Assessment Tool
SCAT	Standardized Concussion Assessment Tool
SCOAT	Sports Concussion Office Assessment Tool
TBI	Traumatic brain injury
TE	Echo time
TR	Relaxation time
TT Mapping	Transient Time Mapping
UADE	Unanticipated adverse device effect
WAIS	Wechsler Adult Intelligence Scale
WISC-IV	Wechsler Intelligence Scale for Children–Fourth Edition, fourth edition
WMI	WAIS-IV/WISC-IV Working Memory Index

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APPENDIX 1 – STUDY SITE AND INVESTIGATOR LIST

The following investigators at each study site will be responsible for the conduct of this study:

Investigator(s):*	**Site 001**	**Teena Shetty, MD** (Principal Investigator) *Tel:* 1 (212) 774-2138 *e-mail*: shettyt@hss.edu	Hospital for Special Surgery (HSS) 525 East 71st Street, Belaire 5th floor New York, NY 10021 US
	Site 002	**Pratik Mukherjee, MD, PhD** (Principal Investigator) *Tel*: 1 (415) 750-2146 *e-mail*: pratik.mukherjee@ucsf.edu	University of California at San Francisco (UCSF) 185 Berry Street, Lobby 6 San Francisco, CA 94121 US
	Site 003	**Joseph C Masdeu, MD, PhD** (Principal Investigator) *Tel*: 1 (713) 441-1150 *e-mail*: jcmasdeu@houstonmethodist.org	Houston Methodist Neurological Institute 6560 Fannin Street, Scurlock 802 Houston, Texas 77030 US
	Site 004	**Michael Collins, PhD** (Co- Principal Investigator) *Tel*: 1 (412) 432-3668 *e*-mail: collinsmw@upmc.edu **Anthony P. Kontos, Ph.D.** (Co-Principal Investigator) Tel: 1 (412) 432-3725 Email: akontos@pitt.edu	University of Pittsburgh Medical College 3200 South Water St. Pittsburgh, PA 15203 UPMC Sports Medicine Concussion Program Department of Orthopedic Surgery University of Pittsburgh 200 Lothrop St Pittsburgh, PA 15213-2582
	Site 005	**Gillian A. Hotz, PhD** (Principal Investigator) *Tel*: 1 (305) 243-4004 *e*-mail: ghotz@med.miami.edu	University of Miami Hospital Lois Pope Life Center 1095 NW 14th Terrace Miami, FL 33136
	Site 006	**Michael McCrea, PhD, ABPP-CN** (Principal Investigator) *Tel*: 1 (414) 955-7302 *e*-mail: mmccrea@mcw.edu	Medical College of Wisconsin Department of Neurosurgery 9200 West Wisconsin Avenue, Milwaukee, Wisconsin 53226
	Site 008	**Roland Lee, MD** (Principal Investigator) *Tel*: 1 (619) 543-6766 *e-mail*: rrlee@ucsd.edu	University of California, San Diego Radiology/RIL, 9500 Gilman Drive, MC 0852, La Jolla, CA 92093-0852
	Site 009	**Thomas M. Talavage, PhD** (Principal Investigator) *Tel*: 1 (765) 494-5475 *e-mail*: tmt@purdue.edu	Purdue University School of Electrical & Computer Engineering 465 Northwestern Ave West Lafayette, IN 47907-2035
	Site 010	**Jeffery J. Bazarian, MD, MPH** (Principal Investigator) *Tel*: 1 (585) 275-2909 *e-mail*: Jeff_Bazarian@URMC.Rochester.edu	University of Rochester Medical Center Department of Emergency Medicine, 265 Crittenden Blvd, Box 655C, Rochester, NY 14642

* The identifier Site 007 was reserved for a site no longer participating in the study.

APPENDIX A – SEGMENT 0 VOLUNTEER SCAN LOG

Segment 0 volunteers may be enrolled for training/retraining purposes only.

Date	**Site ID**	**Volunteer No.**	**Scanner ID** (if multiple scanners used for study at site)	**Volunteer is Eligible** (per Segment 0 inclusion/ Exclusion and criteria for repeat scanning)	**Sponsor representative present during scanning** (Yes/No)	**Scan completed** (Yes/No)	**If no, reason not completed**	**Coil Used** (if used, specify make/ manufacturer)	**Scan Operators Comments**

APPENDIX B – FMRI QA COMPLETION LOG

This appendix is removed as per Amendment to protocol version 1.0 to 2.0 amendment ID Nos. #7 and #9. This log is no longer used as part of this study.

APPENDIX C – SCREENING AXIS I/II DISORDERS (EXCLUSION CRITERIA)

Table C-1: Screening Criteria for Exclusion of Subjects with DSM-IV Axis I and II Disorders

Inclusion/Exclusion clarification	Additional Screening Requirements (if requirements cannot be met, the subject should be excluded)	Axis	Disorder
May be Included*	Clinical diagnosis of Major Depressive Disorder (MDD) should be excluded. If a subject self-reports depression without MDD diagnosis, subject should be included if screening **Hamilton Score** (http://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf; *Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62*) is within normal ranges (0-19). Scores of ≥20 are excluded (indicating moderate, severe, or very severe depression)	Axis I	Depression
May be Included*	If a subject self-reports anxiety, screening should include a **Zung Self-Rating Anxiety Scale**, a rapid and validated assessment developed by Duke and including 20 questions (Zung WWK. A rating instrument for anxiety disorders. Psychosomatics. 1971; 12(6): 371-379).	Axis I	anxiety disorders
Excluded	N/A	Axis I	bipolar disorder
May be Included*	Subjects should be excluded if currently receiving prescription medication for the disorder (may be included if not currently be treated) **AND** the response to "Does the disorder limit your functioning in routine daily occupational or personal activities?" is YES based on self-response. (**Note**: *Both criteria should be met for exclusion*)	Axis I	ADHD, autism spectrum disorders
Excluded	N/A	Axis I	autism
Excluded	N/A	Axis I	anorexia nervosa
Excluded	N/A	Axis I	bulimia nervosa
Excluded	N/A	Axis I	schizophrenia
Excluded	N/A	Axis I	Other condition
May be Included*	Subjects should be excluded if currently receiving prescription medication for the disorder (may be included if not currently be treated) **AND** the response to "Does the disorder limit your functioning in routine daily occupational or personal activities?" is YES based on self-response. (**Note**: *Both criteria should be met for exclusion*)	Axis II	narcissistic personality disorder, histrionic personality disorder, avoidant personality disorder, dependent personality disorder, obsessive-compulsive, personality disorder intellectual disabilities
Excluded	N/A	Axis II	paranoid personality disorder
Excluded	N/A	Axis II	schizoid personality disorder
Excluded	N/A	Axis II	schizotypal personality disorder
Excluded	N/A	Axis II	borderline personality disorder
Excluded	N/A	Axis II	antisocial personality disorder
Excluded	N/A	Axis II	other disorders

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APPENDIX D – DETAIL OF POST-PROCESSING ASSESSMENT MODULES

Post-Processing Assessment Document Version: 1.0 [Protocol Amendment 4.0]
Sponsor Release Date: 14/Nov/2016
Date Received by PI: _____

_____ _____
Printed Name of Principal Investigator Printed Name of Sponsor Representative

_____ _____
Signature of Principal Investigator Signature of Sponsor Representative

Module Number	Module Title	Assessments	Assessor	Output type	Assessment Instructions	Type of Stored Files
1	Volumetry Post-Processing Module	1. Whole brain 2. Parenchyma 3. Supratentorial region 4. Cortical gray matter 5. Hippocampus 6. Thalamus 7. Caudate nucleus (labeled as 'Caudate' on device the report) 8. Putamen 9. Globus pallidus (labeled as 'Pallidum' on device report) 10. Amygdala	technician (non-radiologist)	Numerical	Record the numerical output for each anatomical region as cubic centimeters (cm^3)	1. DICOM 2. P-files 3. Auxiliary data (if applicable)
2	Kurtosis Post-Processing Module	1. ADC 2. eADC 3. FA 4. OrthoK 5. ParK 6. MuMinK 7. MuMaxK 8. AKC min 9. AKC max 10. Mean K 11. FA-K 12. Color FA	N/A	Twelve (12) electronic quantitative image maps and one (1) corrected diffusion weighted image set	No assessments conducted	1. DICOM 2. P-files 3. Auxiliary data (if applicable)

3	RS fMRI Post-Processing Module	1. Default Mode Network 2. Primary Visual Network 3. Secondary visual 4. Left motor (hand) 5. Right motor (hand) 6. Left motor (face) 7. Right motor (face) 8. Dorsal attention system 9. Executive control network (left) 10. Executive control network (right) 11. Salience network	N/A	Thirteen (13) seed-based and thirty (30) ICA-based network images	No assessments conducted	1. DICOM 2. P-files 3. Auxiliary data (if applicable)
4	RSI Post-Processing Module	1. free water 2. neurite density	N/A	two (2) electronic quantitative image maps of the brain	No assessments conducted	1. DICOM 2. P-files 3. Auxiliary data (if applicable)
5	QSM Post-Processing Module	susceptibility	N/A	One electronic quantitative image map	No assessments conducted	DICOM
6	SWI combined echo	susceptibility	Radiologist	Images	Check for microbleeds (instructions on the reader report form)	1. DICOM 2. P-files 3. Auxiliary data (if applicable)
7	MR Spectroscopy	Metabolite ratios	Technician	N/A (numerical values already produced by scanner-based processes)	From the DICOM viewed on AW, record each bilateral value (na, cr, ch, mi, h2o)	DICOM Text file

APPENDIX E – DATA COLLECTION BY STUDY VISIT

Detail of Data Collection by Study Visit Version: 4.0
Sponsor Release Date: 14/Nov/2016
Date Received by PI: _____

_____ _____
Printed Name of Principal Investigator Printed Name of Sponsor Representative

_____ _____
Signature of Principal Investigator Signature of Sponsor Representative

Key: Applicable data points are marked by segment, where 1 = Segment 1 mTBI patients, 2 = Segment 2 non-mTBI controls, 0 = volunteers for training.

Note: The intervals of each visit are defined in Protocol Table 2. Screening for enrollment eligibility should occur before Visit 1 begins, and may be conducted in advance or immediately prior to the start of Visit 1 in accordance with site recruitment practices. Screening and Visit 1 may occur on the same day id the protocol requirements are met.

	Visits (Clinical Site)				
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Eligibility					
Eligibility per the inclusion criteria/ Exclusion criteria	0,1,2				
MR Safety Screening		0 (*all visits*),1,2	1,2	1,2	1,2
Screening completion for eligibility (if applicable)	1,2				
Hamilton Score	1,2				
Zung Score	1,2				
DAST-10	1,2				
AUDIT C [2]	1,2				
Written informed Consent	0,1,2				
Baseline medical and demographic data					
Baseline characteristics (i.e. vital signs)		1,2	1,2	1,2	1,2
History of prior concussion		1,2			
If applicable, relevant prior TBI-related medical records may be collected and provided to the Sponsor. For each prior TBI the following should be collected:		1,2			
Clinical notes describing the case by the site PI or		1,2			

FOOTNOTES CORRESPONDING TO NUMERALS IN THE TEXT

[2] In the event that all points come from AUDIT C question #1, the investigator will determine eligibility based on his or her medical judgment.

	Visits (Clinical Site)				
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
clinical neurologist (*mandatory* if a prior TBI event is reported)					
Neuroimaging (when available)		1,2			
Baseline cognitive assessments like SCAT2/3 or other neuropsychological (when available)		1,2			
Prior TBI-related medical records and/or laboratory reports (when available)		1,2			
Certainty of mTBI diagnosis on a 3 point ordinal scale, where 1 = certain mTBI diagnosis, 2 = probable mTBI diagnosis, 3 = possibly mTBI diagnosis) (as defined in Section 6.3.3. Baseline Data Collection: Certainty of Diagnosis)	1				
How much sleep did you have last night (hr)		1,2	1,2	1,2	1,2
History of exposure to contact sports		1,2	1,2	1,2	1,2
NINDS CDE Tools[3] (*versions used may be updated if new versions are released during the study or for other research purposes*)					
TBI Type, Place, Cause (TBI CDE Version 4.0)	1				
Injury Presentation (TBI CDEs Version 4.0)	1				
Post-injury status (TBI CDEs Version 5.0)	1				
Medical history (to include prior TBI history)		1,2	1,2 (changes since last visit/recent use)	1,2 (changes since last visit/recent use)	1,2 (changes since last visit/recent use)
General Core version 1.0	1,2				
Language spoken	1,2				
Socioeconomics (TBI CDE Version 5.0)	1,2				

FOOTNOTES CORRESPONDING TO NUMERALS IN THE TEXT

[3] The National Institute of Neurological Disorders and Stroke (NINDS) and several Co-sponsoring Federal agencies have the common mission of developing data standards for clinical research, resulting in production of the NINDS Common Data Elements (CDE) worksheets for assessment of Traumatic Brain Injury (TBI) by the CDE Working Groups for all ages and severities (August 2013 Version; http://www.commondataelements.ninds.nih.gov). Some assessments may be used in a modified form for research purposes or may be updated if new versions become available during the study. Consult the Sponsor-provided CRF for specific line items of the GE adaptations to these forms.

	Visits (Clinical Site)				
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Medication, stimulant, or illicit substance		1,2	1,2 (changes since last visit)	1,2 (changes since last visit)	1,2 (changes since last visit)
Additional elements					
How much sleep did you have last night?		1,2	1,2	1,2	1,2
History of exposure to contact sports (sports played, position, dates)		1,2	1,2	1,2	1,2
Clinical Assessments					
Symptoms self-report					
Rivermead Post-Concussion Symptoms (PCS) Questionnaire		1,2	1,2	1,2	1,2
Cognitive Behavioral					
GOS-E [4]		1,2	1,2	1,2	1,2
BSI-18		1,2	1,2	1,2	1,2
GCS-E [5]		1,2	1,2	1,2	1,2
Trail Making Test (TMT) Parts A & B		1,2	1,2	1,2	1,2
WISC-IV or WAIS-IV (*based on age of subject*) WMI and PSI composite scores, requiring subtests:					
Digit span (WMI component)		1,2	1,2	1,2	1,2
Letter-numbering sequence (WMI component)		1,2	1,2	1,2	1,2
Coding (PSI component)		1,2	1,2	1,2	1,2

FOOTNOTES CORRESPONDING TO NUMERALS IN THE TEXT

[4] *Glasgow Outcome Scale Extended (GOS-E)*. The Glasgow Outcome Scale (GOS) is a global scale for functional outcome that rates patient status into one of five categories: Dead, Vegetative State, Severe Disability, Moderate Disability or Good Recovery. The Extended GOS (GOSE) provides more detailed categorization into eight categories by subdividing the categories of severe disability, moderate disability and good recovery into a lower and upper category. Extended Glasgow Outcome Scale (GOS-E) ratings are shown below. Use of the structured interview is recommended to facilitate consistency in ratings.

1. Death
2. Vegetative state
3. Lower severe disability
4. Upper severe disability
5. Lower moderate disability
6. Upper moderate disability
7. Lower good recovery
8. Upper good recovery

Accessed online at www.tbi-impact.org/cde/mod_templates/12_F_01_GOSE.pdf 08/Sep/2015

[5] Nell et al. An extended Glasgow Coma Scale (GCS-E) with enhanced sensitivity to mild brain injury. Arch Phys Med Rehabil. 2000 May;81(5):614-7.

	Visits (Clinical Site)				
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Symbol Search (PSI component)		1,2	1,2	1,2	1,2
HVLT-R		1,2	1,2	1,2	1,2
Physical Tests					
BESS [6]		1,2	1,2	1,2	1,2
MR Data (Clinical Site)					
MR Scanner Information					
System ID		1,2	1,2	1,2	1,2
Model of MR Scanner		1,2	1,2	1,2	1,2
MR in/out time (exposure time on 24 hr clock)		1,2	1,2	1,2	1,2
GE Research Pack II Scan					
MR Data					
DICOM		1,2	1,2	1,2	1,2
P-files		1,2	1,2	1,2	1,2
Auxiliary files					
MR Scan information					
MR in/out time (exposure time on 24 hr clock) [7]		1,2	1,2	1,2	1,2
Make/model of any MR accessories used		1,2	1,2	1,2	1,2
MR Coils used					
32-channel (Nova Medical) coil use/identity		1,2	1,2	1,2	1,2
Conventional coil make/model		1,2	1,2	1,2	1,2
Errors (Y/N) and comments					
Site Radiologist Reads of T1, T2, Flair, and reconstructed SWI and DTI Acquisitions (NINDS TBI CDE Version 4.0)		1,2	1,2	1,2	1,2
MR Post-processing (processed at Imaging Laboratory for data from indicated visits)					
Post-processing assessment modules and evaluations (Appendix D)		1,2	1,2	1,2	1,2

Note: In the event that updates to assessments are elements are required during the course of the study, the Sponsor may provide an updated listing to the sites for use in this study.

FOOTNOTES CORRESPONDING TO NUMERALS IN THE TEXT

[6] The BESS should be performed on a firm surface. Foam pads should not be used for BESS testing in this study.

[7] Exposure time (T_e) is estimated by subtracting the MR scanning time in from MR scanning time out (T_i and T_o, respectively), as given by $T_e = T_o - T_i$

APPENDIX F – AMENDMENT TO PROTOCOL VERSION 1.0 TO 2.0

Purpose: This amendment document describes the changes from protocol version 1.0 to 2.0, as follows:

1. To remove a non-participating site (University of Michigan).
2. To remove the MR phantom daily and monthly sub-studies. Notably, MR phantoms may still be used in routine training and calibration for the study, as originally described in the protocol version 1.0, to ensure quality; however, no systematic data collection will be performed for this data.
3. To clarify language in Appendix E regarding description and identify of cognitive and symptoms assessments.

The following amendments were made to version 1.0 to produce version 2.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td>1</td><td>Study Synopsis</td><td>
<table>
<tr><td><s>Site 007</s></td><td><s>Jeffrey S. Kutcher, MD (Principal Investigator)
Tel: 734-936-9055
e-mail: jkutcher@med.umich.edu</s></td><td><s>University of Michigan
2301 Commonwealth Blvd.
An Arbor, MI 48105</s></td></tr>
</table>
[Footnote added] 1. The University of Michigan Site (originally Site 007) is removed due to non-participation.
<table>
<tr><td>Study Sponsor: GE Healthcare (GEHC)
Sponsor Contact: John Strohmeyer, Senior Clinical Affairs Project Manger</td><td>Address: <s>3200</s> 3000 N Grandview Blvd Waukesha, WI 53188
Telephone: +1-609-865-7423
E-mail: John.Strohmeyer@ge.com</td></tr>
<tr><td>Research Manager Name:
Amy Gallenberg
Clinical Study Program Manager,
GE/NFL Head Health Initiative</td><td>Address: 3200 N Grandview Blvd Waukesha, WI 53188
Telephone: +1-262-409-0704
E-mail: Amy.Gallenberg@med.ge.com</td></tr>
<tr><td>Medical Monitor Name:
Victor Miranda, MD
Executive Medical Director</td><td>Address: <s>3200</s> 3000 N Grandview Blvd Waukesha, WI 53188
Telephone: +1-262-544-3633
E-mail: Victor.Miranda@ge.com</td></tr>
</table>
</td><td>Removed a non-participating site (University of Michigan) from the synopsis site lists.

Updated street address of Sponsor contact.</td></tr>
<tr><td>2</td><td>Study Synopsis - Summary of Study Procedures:</td><td><s>Daily fMRI QA (performed before the start of human scanning on each scan day) and monthly system phantom and, if determined necessary by the Sponsor, monthly diffusion phantom scanning will be performed to verify MR system stability and characteristics throughout the study.</s></td><td>Removed reference to the MR phantom daily and monthly sub-studies.</td></tr>
</table>

Item	Section	Revision or Clarification	Justification
3	Study Synopsis - Device/Product Description:	Site-owned Discovery MR750 3.0T and/or MR750w 3.0T scanners with research coils will be used for acquisition, and commercially available VolumeShare 5 Advantage Workstations (AW) will be used for post-processing. Conventional accessory/ancillary devices, such as alternative MR coils, padding, communication, and safety devices may be provided by the site for use in this study (or by the sponsor, if unavailable for use at any investigational site). ~~The Sponsor will provide MR imaging phantoms necessary for study quality assurance procedures.~~	Removed reference to devices the MR phantom daily and monthly sub-studies for quality assurance.
4	Section 2.1.1. GE Research Pack II Advanced MRI Application Suite	*GE Research Pack II* is an advanced MRI application suite developed by the Sponsor, GE Healthcare (GEHC), consisting of acquisition software executable on Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners and a comprehensive set of post-processing modules (volumetry, Kurtosis, RS fMRI, RSI, and, as applicable, further advanced modules) executable on VolumeShare 5 Advantage Workstations (AW). Acquisition includes pulse sequences and corresponding interface software to define radio frequency (RF), gradient pulses, and associated parameters to optimally shape gradient waveforms when used in conjunction with head coils. Echo time as well as imaging parameters for contrast and other characteristics have been enhanced for optimal results in mTBI based on commercially available MR sequences, including a variety of advanced modules like functional MRI (fMRI), transit time mapping (TT mapping), enhanced arterial spin labeling (eASL), 3D-enhanced T2* weighted angiography (eSWAN), and fluid attenuated inversion recovery (FLAIR), as well as specialized T1 and T2 sequences. <u>To maintain and calibrate systems and for training, routine MR accessories such as MR imaging phantoms, may be used in this study.</u> <u>[18, 19]</u>	Clarified that MR phantoms may still be used in routine training and calibration for the study, as originally described in the protocol version 1.0, to ensure quality; however, no systematic data collection will be performed for this data.
5	Section 2.1.3 MR Imaging Phantoms	~~2.1.3 MR Imaging Phantoms~~ ~~MR Quality Imaging Phantom Models (Quantitative Diffusion Phantom [19] and Quantitative System Phantom [20]; High Precision Device, Inc., Boulder, CO, USA) are modeled after the human head imaging characteristics. The Quantitative Diffusion Phantom consists of a sphere containing small areas of varied contrast agents designed for quantitative standardization, including recording of the apparent diffusion coefficient (ADC). The Quantitative System Phantom is a plastic sphere containing vials of varied polymer polyvinylpyrrolidone (PVP) aqueous solutions for standardization of isotropic diffusion in H_2O, designed for measuring B_1 uniformity, B_0 uniformity, geometric linearity, gradient amplitude, slice profile, slice positioning accuracy, landmark accuracy, system center frequency drift (short time duration), resolution, signal-to-noise ratio (SNR), and accuracy/precision of T1 and T2 measurements.~~	Removed reference to devices the MR phantom daily and monthly sub-studies for quality assurance.
6	Section 4.2. Type of Research Study	*This study plans to include <u>up to</u> seven (7) <u>sites</u>*	Revised to match synopsis language. There are currently 6

Item	Section	Revision or Clarification	Justification
			active sites, but up to 7 may participate.
7	Section 6.1.2. MR Imaging Phantoms (monthly procedure)/ Section 6.1.2 fMRI Quality Assurance (QA) Tool (daily procedure)	~~**6.1.1 MR Imaging Phantoms (monthly procedure)**~~ ~~To enable future evaluation of performance between scanners and reproducibility of findings, each site will perform MR Imaging Phantom Model scans (*Quantitative System Phantom* and, if determined necessary by the Sponsor, *Quantitative Diffusion Phantom*, as described in Section 3.1.3 MR Imaging Phantoms) at least once per month (at intervals of 30±5 days). Monthly phantom scans will be completed in accordance with the manufacturer's instructions and, if necessary, additional scanning instructions provided by the Sponsor.~~ ~~For each phantom scan performed as part of the quality procedure, study staff will record the DICOM output and provide results to the Sponsor for regular technical processing and review. Additional MR imaging phantom scanning may be conducted at any time during the study (except during a clinical scan of a human subject), at the discretion of the investigator. If the investigator observes any issues that he or she suspects could interfere with the intended function or performance of the device, the Sponsor should be informed.~~ ~~**6.1.2 fMRI Quality Assurance (QA) Tool (daily procedure)**~~ ~~fMRI is inherently sensitive to minor and expected variations in local systems that do not typically impact clinical scanning. In order to ensure the integrity of fMRI data, at the start of each day of study scanning, prior to the first scan of a human subject the fMRI Quality Assurance (QA) tool should be executed on each scanner used in the study. This procedure is conducted with no human in the bore. Completion of the fMRI QA procedure should be logged in the fMRI QA Completion Log, as shown in Appendix B – fMRI QA Completion Log.~~	Removed the procedures for MR phantom daily and monthly sub-studies.
8	Section 7.0 Training Plan	Training plan documents and logs of training attendance will be stored in the Sponsor's clinical history file (CHF).	Clarified that there is a separate training plan, to be stored in the HAT file.
9	Section 7.1. Training Plan for Research Device	The Sponsor will provide training on the research device and any device optimizations or versions released during the study. The Investigator may request that additional training be provided to staff by the Sponsor or previously trained study staff during the study. MR imaging phantoms may be used in training and retraining during this study, and phantom training data may be collected and disclosed to the Sponsor as part of this study.	Clarified that MR phantoms may still be used as part of training and, though not systematically collected, any such data may be disclosed to the Sponsor as part of research.
10	Section 13.4. Record Retention at the Site	▪ Subject Files – containing the completed subject CRFs, (signed/dated) Informed Consent Form(s)	Corrected typographical error. This should read that

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>▪ Regulatory Binder – containing the protocol and amendments, EC/IRB submissions and approvals, (blank ~~and signed/dated~~) Informed Consent Form(s), Site study logs and sub-contracted site qualifications and contracts.</td><td>signed ICFs are stored in subject files (not the regulatory binder). The regulatory binder will contain copies of blank ICF versions.</td></tr>
<tr><td>11</td><td>Section 16.1. Abbreviations and Terminology</td><td>UADE Unanticipated adverse device effect</td><td>Added abbreviation.</td></tr>
<tr><td>12</td><td>Appendix A – Segment 0 Volunteer Scan Log</td><td>Segment ~~1~~ 0 volunteers may be enrolled for training/retraining purposes only.</td><td>Corrected typographical error in the instruction, referencing Segment 0 (volunteers).</td></tr>
<tr><td>13</td><td>Appendix B – fMRI QA Completion Log</td><td>Appendix B – fMRI QA Completion log
This appendix is removed as per Amendment to protocol version 1.0 to 2.0 amendment ID Nos. #7 and #9. This log is no longer used as part of this study.
~~[content tables of log removed]~~</td><td>Removed the log corresponding to MR Phantom procedures, which are removed per amendment #7.

The Appendix B header is maintained to keep the alphanumeric order of appendices consistent.</td></tr>
<tr><td>14</td><td>APPENDIX E – DATA COLLECTION BY STUDY VISIT</td><td>
<table>
<tr><th></th><th colspan="5">Visits (Clinical Site)</th></tr>
<tr><th></th><th>Screening</th><th>Visit 1</th><th>Visit 2</th><th>Visit 3</th><th>Visit 4</th></tr>
<tr><td colspan="6">Eligibility</td></tr>
<tr><td>…</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>AUDIT C [2]</td><td>1,2</td><td></td><td></td><td></td><td></td></tr>
<tr><td>…</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Baseline medical and demographic data</td></tr>
<tr><td>Certainty of mTBI diagnosis on a 3 point ordinal scale, where 1 = certain mTBI diagnosis, 2 = probable mTBI diagnosis, 3 = possibly</td><td>1</td><td>~~1~~</td><td></td><td></td><td></td></tr>
</table>
</td><td>Clarifies the procedures to be completed, including footnotes as reference to scales. Removed the SCAT GSC and added GOS-E.

Moved certainty of diagnosis to screening visit, per logistical recommendation by CRO.

Added that recent substance/alcohol use would be recorded, in addition to changes in status.</td></tr>
</table>

		mTBI diagnosis)						
		…						
		Clinical Assessments						
		…						
		~~SCAT2 Graded Symptoms Checklist~~GOS-E [4]		1,2	1,2	1,2	1,2	
		BSI-18		1,2	1,2	1,2	1,2	
		GCS-E [5]		1,2	1,2	1,2	1,2	
		…						
		Medical history (to include prior TBI history)		1,2	1,2 (changes since last visit/recent use)	1,2 (changes since last visit/recent use)	1,2 (changes since last visit/recent use)	
		…						
		MR Data (Clinical Site)						
		…						
		~~**Per-sequence information**~~						
		~~Frequency Field of View (FFOV)~~		~~1,2~~	~~1,2~~	~~1,2~~	~~1,2~~	
		~~Phase Field of View (PFOV)~~		~~1,2~~	~~1,2~~	~~1,2~~	~~1,2~~	
		~~Ease of use (1-5 Likert)~~[6]						
		…						

[added footnote] 2. In the event that all points come from AUDIT C question #1, the investigator will determine eligibility based on his or her medical judgment.

[added footnote] 4. *Glasgow Outcome Scale Extended (GOS-E).* The Glasgow Outcome Scale (GOS) is a global scale for functional outcome that rates patient status into one of five categories: Dead, Vegetative State, Severe Disability, Moderate Disability or Good Recovery. The Extended GOS (GOSE) provides more detailed categorization into eight categories by subdividing the categories of severe disability, moderate disability and good recovery into a lower and upper category. Extended Glasgow Outcome Scale (GOS-E) ratings are shown below. Use of the structured interview is recommended to facilitate consistency in ratings.

1. Death
2. Vegetative state
3. Lower severe disability
4. Upper severe disability

Removed per-sequence information duplicated in DICOM and ease of use assessment, which does not directly support study aims.

Note that coil information should be recorded per case, but should be 32-ch nova coil for most patients (unless unable to use for medical reasons).

Item	Section	Revision or Clarification	Justification
		5. Lower moderate disability 6. Upper moderate disability 7. Lower good recovery 8. Upper good recovery Accessed online at www.tbi-impact.org/cde/mod_templates/12_F_01_GOSE.pdf 08/Sep/2015 [added footnote] 5. Nell et al. An extended Glasgow Coma Scale (GCS-E) with enhanced sensitivity to mild brain injury. Arch Phys Med Rehabil. 2000 May;81(5):614-7. [removed footnote 6 corresponding to removed assessment] ~~Five point Likert scale (1-5) scale for "How easy is the pulse sequence to use?", rated as follows:~~ ~~1 – Very easy to use~~ ~~2 – Easy to use~~ ~~3 – Neutral~~ ~~4 – Difficult to use~~ ~~5 – Very difficult to use~~	

APPENDIX G – AMENDMENT TO PROTOCOL VERSION 2.0 TO 3.0

Purpose: This amendment document describes the changes from protocol version 2.0 to 3.0, as follows:

1. To clarify language surrounding study enrolment, data collection, and withdrawal. These are clarifications to the original procedure designed to improve consistency of execution across sites and do not alter the scientific intent of the original procedures.
2. To add specific definition around for scoring on the existent 3-point diagnostic certainty scale and baseline data collection.
3. To clarify terminology related to devices and software, including which will clinically useful sequences can be read by study readers.
4. Clarifies that patients that experience a second TBI or other severe injury that could interfere with the study during their enrolment should be withdrawn.
5. Updates Appendix D with most current post-processing details.

The following amendments were made to version 2.0 to produce version 3.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

Item	Section	Revision or Clarification	Justification
15	Study Synopsis: Summary of Study Procedures	**Summary of Study Procedures:** *Clinical Site Procedures*: Two parallel subject segments will be enrolled, including (1) mTBI patients with recent injury in Segment 1 and (2) subjects without recent TBI injury of similar age and demographic characteristics (non-TBI controls in Segment 2). Baseline health information, demographics, and medical history (including prior TBI injury) will be collected for both segments. Subjects will attend up to four sequential visits relative to injury date (mTBI subjects) or first study scan date (controls): Visit 1 = ≤72 hr, Visit 2 = 7±2 days, Visit 3 = 14±2 days, and Visit 4 = 90±7 days. The mTBI subjects (Segment 1) may start at Visit 1 or Visit 2. Each visit will include a clinical neuropsychological assessment battery and MR scan with *GE Research Pack II* (including research sequences and clinically useful T1, T2, Flair, and reconstructed SWI and DTI~~SWAN~~) will be evaluated by the site. *Laboratory Procedures*: Clinically acquired MR data (DICOM, P-files, and auxiliary files) will be transferred to an imaging laboratory for *GE Research Pack II* reconstruction of clinically useful views using multiband technology and study post-processing. Post-processed data and evaluations (as indicated on a per-module basis by the Sponsor) will be collected.	Clarifies multiband and processing views from the study may be clinically useful.
16	Study Synopsis: Device/Product Description	**Device/Product Description:** The device under study is the *GE Research Pack II* advanced MRI application suite developed by the Sponsor, GE Healthcare (GEHC), which consists of acquisition software executable on commercially available Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners and software for multiband image reconstruction and ~~and~~ post-processing features ~~modules~~ (volumetry, Kurtosis, RS fMRI, RSI,	Clarified language describing study software modules for consistency of terminology.

Item	Section	Revision or Clarification	Justification
		and, as applicable, further advanced modules) executable on commercially available image processing workstations. *GE Research Pack II* is optimized for use with the investigational 32-channel head coil for 3.0T GE scanners (Nova Medical). Site-owned Discovery MR750 3.0T and/or MR750w 3.0T scanners with research coils will be used for acquisition, and commercially available VolumeShare 5 Advantage Workstations (AW) will be used for reconstruction and post-processing. Conventional accessory/ancillary devices, such as alternative MR coils, padding, communication, and safety devices may be provided by the site for use in this study (or by the sponsor, if unavailable for use at any investigational site).	
17	Section 2.1.1. GE Research Pack II Advanced MRI Application Suite	*GE Research Pack II* is an advanced MRI application suite developed by the Sponsor, GE Healthcare (GEHC), consisting of acquisition software executable on Discovery MR750 3.0T/Discovery MR750w 3.0T MR scanners. The software enables routine reconstruction of images using multiband technology as well as study-specific post-processing of other types of information not typically found in clinical images. ~~*and a*~~*GE Research Pack II* will include a comprehensive set of post-processing modules (volumetry, Kurtosis, RS fMRI, RSI, and, as applicable, further advanced modules) executable on VolumeShare 5 Advantage Workstations (AW).	Clarifies which views from the study are clinically useful for evaluable by the site.
18	Section 2.1.2. 32-channel Multiband MR Brain Coil	**2.1.2 32-channel Multiband MR Brain Coil** The 32-channel multiband MR brain coils are designed to speed up scan time with parallel imaging. *GE Research Pack II* is optimized for the 32-channel MR brain coil for GE 3.0T (Nova Medical, Wilmington, Massachusetts, USA). [20]	Clarified terminology, for consistency.
19	Section 2.1.4. VolumeShare 5 Advantage Workstation (AW)	Post-processing is completed on a VolumeShare 5 Advantage Workstation (AW), which supports image display, manipulation, reconstruction, post-processing, and selective recording and is intended to be used to create and review diagnostic evidence related to radiology procedures by trained and licensed physicians and/or qualified clinical/medical personnel.	Clarified terminology, for consistency.
20	Section 2.2. Regulatory Status	*GE Research Pack II*, including its acquisition and software (multiband reconstruction and post-processing components), and the 32-channel multi-band MR brain coil for GE 3.0T (Nova Medical) are investigational MRI system components that are not currently cleared by the US FDA.	Clarified terminology, for consistency.
21	Section 2.4.2. Issuance of Devices to Imaging Laboratories	If not already available at laboratories ~~conducting~~ executing *GE Research Pack II* ~~post-processing~~ software, ~~,~~ the Sponsor may provide VolumeShare 5 Advantage Workstation (AWs) for study use. The unique identification information for study devices will be recorded. The Sponsor will provide, install, and configure *GE Research Pack II* ~~post-processing~~ software on these workstations, and, as deemed necessary by the Sponsor, provide training for the use, quality check, and maintenance of these devices.	Clarified terminology, for consistency.

Item	Section	Revision or Clarification	Justification
22	Section 5.1.1. Enrollment of non-mTBI controls	**Enrollment Rate:** Each site should enroll approximately half as many control subjects as mTBI subjects, at a rate of approximately one control enrollment for each two mTBI subjects that complete at least two visits (1:2). Though it is prospectively expected that actual enrollment rates may vary, it is the investigator's responsibility to maintain this approximate rate in order to minimize possible bias due to variance in scanner performance ("scanner drift") and other possible confounders. ~~that complete two consecutive visits and thus provide two consecutive data points (complete either Visits 1 and 2, or Visit 3 and 4), e.g., one control may be enrolled for every two mTBI subjects.~~ **Population Matching:** The study aims to achieve overall matched mTBI and control populations across sites. The overall population will be matched for characteristics identified in order of priority in Table 2. To enable sites to select control subjects that match the overall population, a report of mTBI subject enrollment will be generated by the Sponsor or its delegated contract research organization (CRO) and provided to the site on a rolling monthly basis. The report will categorically detail the number of enrolled mTBI subjects with the following characteristics (Table 2). The clinical site, under the supervision of the Principal Investigator, will be ultimately responsible for ensuring that matched controls are selected according to these criteria. **Case-Control Matching:** When possible, investigators are also encouraged to enroll individually matched mTBI and control cases of potential medical interest. Priority should be given, however, to ensuring an appropriate overall population match. **Overall Population Reports**: ~~A report of mTBI subject enrollment will be generated by the Sponsor or its delegated contract research organization (CRO) and provided to the site on a monthly basis (30±7 days). The report will categorically detail the number of mTBI subjects with the following characteristic characteristics (Table 2). The clinical site, under the supervision of the Principal Investigator, will be ultimately responsible for ensuring that matched controls are selected according to these criteria.~~ Table 2 – Population characteristics for enrollment of non-TBI controls (Segment 2) based monthly mTBI accrual by order of priority for matching ~~Controls are required to attend Visits 1 and 4, but may also attend Visit 2 and 3 when available. Per site, controls should be enrolled in a manner that achieves the same overall ratio within each characteristic category as the mTBI population that has completed two visits to date (per site, all mTBI patients enrolled from study start to date of monthly summary analysis), with the priority indicated above (i.e. highest priority should be given that the control population's overall characteristics resemble those of the mTBI subject population's characteristics for #1, then #2, etc.).~~	Standardized and clarified enrolment of controls procedure.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>23</td><td>Section 5.4.2. Exclusion Criteria by Study Segment</td><td>6. Drug abuse (except marijuana) in past 10 years (if suspected or self-reported confirm by DAST-10 screening);
~~Drug abuse (except marijuana) in past 10 years based on DAST-10 screening;~~

7. Alcohol abuse (if suspected or self-reported confirm by AUDIT-C screening);
~~Alcohol abuse based on AUDIT-C screening;~~
…
12. Been prescribed antipsychotic/antiepileptic medications (including for current or past head injury);</td><td>Clarified wording around screening requirements for mTBI subjects in the exclusion criteria. No change in scientific intent.</td></tr>
<tr><td>24</td><td>Section 5.4.2. Exclusion Criteria by Study Segment</td><td>4. Drug abuse (except marijuana) in past 10 years (if suspected or self-reported confirm by DAST-10 screening);
~~Drug abuse (except marijuana) in past 10 years based on DAST-10 screening;~~

5. Alcohol abuse (if suspected or self-reported confirm by AUDIT-C screening);
~~Alcohol abuse based on AUDIT-C screening;~~
…
10. Been prescribed antipsychotic/antiepileptic medications (including for past head injury);</td><td>Clarified wording around screening requirements for control subject in the exclusion criteria. No change in scientific intent.</td></tr>
<tr><td>25</td><td>Section 6.3.1. Visit Schedule</td><td>Each mTBI patient (Segment 1) and non-mTBI control (Segment 2) will attend a series of up to 4 visits (Table 3). Subjects in the mTBI group may enroll and start the study at either Visit 1 or Visit 2 based on date of injury, and non-mTBI control subjects will attend visits on a similar schedule based on date of first study scan. ~~If a subject attends a visit outside of this visit window, this will be considered a protocol deviation and reported in accordance with Section 9.1. - Management of Protocol Deviations.~~ Subjects should attend all study visits, when possible. Controls will be enrolled continuously, as described in Section 5.1.1. Enrollment of non-mTBI controls. When possible, if the site is using more than one MR scanner for study purposes, the same scanner should be used for all visits for a single subject.

Table 3 - Visit schedule for mTBI and non-mTBI control segments
<table><tr><th>Segment</th><th>Description</th><th colspan="4">Visit Schedule</th></tr><tr><th></th><th></th><th>Visit 1</th><th>Visit 2</th><th>Visit 3</th><th>Visit 4</th></tr><tr><td>Segment 1</td><td>mTBI Subjects

(may be enrolled at</td><td>≤72 hr* from injury</td><td>Day 7±2* from injury</td><td>Day 14±2 from injury</td><td>Day 90±7 from injury</td></tr></table></td><td>Clarified language surrounding protocol visits and removed redundant language references deviation definition. This does not change the scientific intent of the study, but it rather intended to clarify the procedure for consistent execution across sites.</td></tr>
</table>

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>either Visit 1 or Visit 2, where first visit is considered baseline)</td><td><u>(Baseline)</u></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td><u>NA</u></td><td><u>Day 7±2* from injury (Baseline)</u></td><td><u>Day 14±2 from injury</u></td><td><u>Day 90±7 from injury</u></td></tr>
<tr><td>Segment 2</td><td>non-mTBI Controls<u>#</u></td><td>Baseline <u>#</u></td><td>Day 7±2 from baseline <u>(optional)</u></td><td>Day 14±2 from baseline <u>(optional)</u></td><td>Day 90±7 <u>#</u> from baseline</td></tr>
<tr><td>Segment 0</td><td>volunteer subjects (training)</td><td colspan="3">Volunteers may participate one or more scans, if they remain eligible and satisfy <u>Section 6.2.2. Participation in Multiple Scan Sessions</u></td></tr>
</table>
Note: Day 0 is based on <u>date of injury</u> for mTBI patients (Segment 1) or the <u>day of first study scan (baseline)</u> for patients without mTBI (Segments 0 and 2). The date of first study scan is considered baseline for all subjects.

* <u>mTBI subjects may be enrolled at either Visit 1 or Visit 2.</u>

<u>#</u> Non-mTBI subjects ~~are required to~~<u>should</u> attend visits 1 and 4, ~~but should attend~~<u>and</u> all 4 visits~~,~~ when possible~~.~~<u>.</u>
</td><td></td></tr>
<tr><td>26</td><td>Section 6.3.2. Handling Visit Completion, Missed Visits, and Loss to Follow-up</td><td><u>First Visit (Baseline):</u> <u>All Segment 1 (mTBI subjects) and Segment 2 (non-mTBI controls) are required to complete their initial MRI scan and clinical neurological assessment within 24 hours (in either order), and are required to satisfy complete all parts of the visit within the visit window as defined in Table 2 (with the exception of requests for medical history and other historical information, which may be requested and added to the subject record at any time during the study, as data becomes available to the investigators). Any subject that is not able to complete all parts of the first visit within the visit window should be withdrawn from study once this becomes known. No additional information will be collected after the time of withdrawal, but information collected up until this point may be used and disclosed. Withdrawal due to inability to complete a visit is not considered a deviation if the subject is immediately removed from study (withdrawn) and no additional information is collected.</u>

<u>Subsequent Visits – Missed or Incomplete Visits:</u> <u>For all subsequent visits, subjects may remain on study if a visit is missed or incomplete for any reason, at the investigator's discretion (else the subject may be withdrawn). The site will note the reason for any missed or incomplete visits for subjects that remain on study, and these incomplete data sets will not considered a deviation. It is ultimately</u></td><td>Added clarifying language to ensure consistent execution of missed visit procedures across sites.</td></tr>
</table>

Item	Section	Revision or Clarification	Justification
		the responsibility of the investigator to ensure that data is maximally complete, as incomplete case data may impair scientific integrity of the study. **Subsequent Visits – Missed Visit Window (Table 2):** If a subject failed to complete a visit within the visit window, he/she may still be eligible to complete future visits as scheduled (Table 2). Except in exceptional circumstances, study procedures should not be conducted outside of the visit windows (Table 2). Any part of a study visit conducted outside of the protocol visit windows should be reported as a deviation. **Lost to Follow-Up**: If a subject is not able to be contacted for scheduled visits (Table 2), the subject will be withdrawn from study and considered lost to follow-up. The site should make reasonable attempts to contact all subjects and document these activities as part of the study source documentation stored in the study file. Subjects lost to follow-up are not considered in deviation of the protocol if documentation of reasonable attempt to contact is maintained by the site and the subject is withdrawal is documented in the study record. **Withdrawal:** Withdrawals should be documented as per Section 6.5. -Withdrawal and Discontinuation Criteria. Once a subject is withdrawn, he/she is no longer eligible to participate in any future study visits or procedures, but the data collected up until the time of withdrawal may still be used and disclosed as part of this research.	
27	Section 6.3.3 Baseline Data Collection	After the subject is determined eligible according to the inclusion/exclusion and has provided informed consent (and assent for minors), ~~he/she will undergo an initial assessment~~the following will be recorded for each subject~~ at the first visit~~: • **~~, wherein g~~General ~~medical~~ Medical H~~h~~istory and De~~de~~mographic ~~information~~Information~~,~~** • **Prior mTBI Information**: Current (*for mTBI subjects*) or prior TBI ~~history~~ information (*~~if applicable~~for all control and mTBI subjects*), if available for the subject (it is prospectively expected that not all data may be available for each subject):~~,~~ ○ prior medical records ○ relevant laboratory reports ○ neuroimaging (including CT, MRI, or other scans) ○ baseline neuropsychological or cognitive assessments done for sports or occupational purposes (such as SCAT2/3 for sports players), which may be requested from prior care providers and collected as part of study data.	Clarifies language around collection of baseline data to match the actual electronic data capture (EDC) implementation. Adds definition around the 3-point scoring for diagnostic certainty to ensure consistent execution across sites.

Item	Section	Revision or Clarification	Justification
		• **Baseline Clinical Information** about the injury (*must be collected within visit window*): ○ injury presentation information ○ ~~, baseline~~ health ~~information~~ assessments (such as vital signs) collected during the visit~~, and~~ ○ ~~***diagnostic certainty***~~ ***Certainty of Diagnosis*** ~~(~~for mTBI patients in Segment 1~~)~~ (assessed on a 3-point ordinal scale). Eligible subjects are required to meet diagnostic criteria for mTBI at the site. In addition, a qualified physician or clinical psychologist on the study staff will assess certainty of diagnosis based on: **4 =** **Certain mTBI Diagnosis**: Presents with a combination of physical, behavioral/emotional, and/or cognitive symptoms (not pre-existing) where recent head injury is strongly expected to play the central causal role. **5 =** **Probable mTBI Diagnosis**: Presents with at least one physical, behavioral/emotional, and/or cognitive symptoms (not pre-existing) where recent head injury can be reasonably expected to play a causal role. **6 =** **Possible mTBI Diagnosis**: Presents with at least one physical, behavioral/emotional, and/or cognitive symptoms (not pre-existing) where it is uncertain whether or not recent head injury plays a causal role (as in the case where symptoms assessment is complicated by other conditions or diagnoses pre-existing mTBI, such as mood disorders, physical disability, or other chronic conditions or medication use). ~~information will be recorded~~ ~~. For subjects with current mTBI or prior TBI injury, prior medical records, neuroimaging (including CT, MRI, or other scans), and available baseline neuropsychological or cognitive assessments done for sports or occupations purposes (such as SCAT2/3 for sports players) may be requested from prior care providers and collected as part of study data.~~ Baseline will be considered the day of the first study scan for all subjects~~.~~, and *Baseline Data* will be inclusive of information collected or requested based on the first visit (*General Medical and demographic information*, and *prior mTBI information*) and information collected at the first visit (*Baseline Clinical Information*). Only *Baseline Clinical Information* is required to be collected and reported within the visit window. Other information, such as medical history and prior records, may be updated in the subject record as it becomes available to the site.	

Item	Section	Revision or Clarification	Justification
28	Section 6.3.4. Visit Procedures (Clinical Neuropsychological Assessment and MR Scan)	Each visit will consist of a Clinical Neuropsychological Assessment of symptoms self-report, cognitive behavioral scales, and physical testing (lasting approximately 60 minutes) and an MR scan session using *GE Research Pack II* acquisition software (lasting approximately 60 minutes). The MR scan should be completed within the interval 24 hours ~~of~~ before or after the Clinical Neuropsychological Assessment (within 4 hours, when possible). The example listing of data collection to be performed at each visit is shown in Appendix E – Data Collection by Study Visit. For MR scanning, study staff should ensure that the subject meets the criteria for MR safety at the site immediately prior to MRI scanning. Subjects will be provided with clothing safe for MRI (such as hospital gowns), hearing protection, and protective devices, per the site's standard of care for MRI scanning. Subjects will be told how to communicate with the operator during scanning, and scanning may be stopped at any time if the subject reports discomfort. All scans will be completed using 32-channel multiband research coil, except in in cases where the 32-channel multiband research coil cannot be used due to: (1) head size, (2) medical conditions, (3) deformities, (4) anxiety, or (5) other medical issues. Alternatively, any commercially available 32-channel MR coil available at the site may be used, and its applicable identifiers (i.e. make, model, etc.) will be recorded.	Terminology updates, for consistency with prior sections.
29	Section 6.3.5. MR Acquisition Data (Clinical Site Procedure)	For each scan session, the scan operator or designee will record parameters as described in the MR Data (Appendix E – Data Collection by Study Visit) to a Sponsor provided case report form (CRF). DICOM, P-files, and auxiliary files (collected according to the instructions provided by the Sponsor) will be recorded for each visit. This data will be transferred to the Sponsor or its identified contract research organization (CRO) for execution of the *GE Research Pack II* software ~~(including multiband reconstruction for SWI and DTI and study post-processing)~~.	While SWI and DTI are clinically useful, this is removed to correct misinterpretation that these are linked with multiband technology.
30	Section 6.3.6. MR Acquisition Image Reads/Evaluations (Clinical Site Procedure)	One or more site radiologist will read the clinically useful sequences ~~from~~ acquired from *GE Research Pack II*. For reading, the clinically useful image set includes both the images produced routinely from the clinical interface (~~(~~T1, T2, and Flair~~,~~) ~~SWAN~~and images that require reconstruction by the software due to use of multiband technology (SWI and DTI). Readers will assess the entire clinically useful image set (T1, T2, and Flair and reconstructed SWI and DTI) ~~MR acquisitions~~ according to the *NINDS CDE Tool: Imaging* with additional Sponsor-provided elements (if necessary) added for research purposes~~,~~. The reader will determine whether each case is normal or abnormal and complete the Sponsor-provided case report form (CRF) for each case.	Clarifies which software used in the study produce images of possible clinical usefulness to the site, as assessable by site readers.

Item	Section	Revision or Clarification	Justification
		~~and the result will be recorded.~~ Readers are not required to be blinded to clinical care. Readers will have access to reconstructions necessary to~~, but will be~~ review the full clinically useful image set (including conventional reconstructions available from the clinical interface and reconstructions of SWI and DTI produced by the GE Research Pack II software, which are not able to be produced on the clinical interface due to use of the investigational multiband technology). Readers will be ~~-~~blinded to other results of post-~~processed~~ processing with *GE Research Pack II*~~.~~.	
31	Section 6.4.1. Incidental Findings	MR imaging in this study is conducted using investigational MR sequences for research purposes. The investigational research sequences are not intended to provide diagnostic information; however, *GE Research Pack II* also contains components that may be useful as reference for the patient's clinical care (including clinically useful T1, T2, Flair, and reconstructed SWI and DTI ~~SWAN~~ MR data ~~conducted during research scan sessions~~). Patient management should not be based solely on data acquired from research sequences. The other research MR images and related data generated as part of study procedures are not intended for use in patient management decisions or to be stored in patient medical records. In the event that a member of the study staff identifies something possibly abnormal in a research MR image that may be of medical significance, they shall notify the principal investigator. The principal investigator will be responsible for evaluating any such incidental findings and, if necessary according to his/her medical judgment, communicating findings to the patient and/or his or her regular physician, in accordance with IRB policy.	Terminology updates, for consistency with prior sections.
32	Section 6.5. Withdrawal and Discontinuation Criteria	A subject may withdraw from study at any time, for any reason without consequence. The Investigator may withdraw a subject at any time for any reason, including some clinical conditions concurrent enrollment in another interventional research study that could confound results or pose risks to the patient, or use any medication, stimulant, or illicit substance that could interfere with safe study conduct or integrity of research data, in the opinion of the Principal Investigator. In the event that a subject experiences an additional TBI injury during the study period or sustains other significant injury that could interfere with study participation or outcomes, the subject should be withdrawn when the investigator becomes aware of the change in the subject's medical status. In cases where the investigator is unsure if an injury would disqualify the subject, the case should be confirmed with the Sponsor's medical monitor. **Note**: For each subject's first visit, the subject must complete their MR scan and neurological assessment per-protocol (baseline and prior medical history data may be collected at any time after enrollment). Thereafter, s~~S~~ubjects that miss a visit or attend a visit outside of the scheduled window should not be withdrawn, and may continue in the study. Missing a visit or visit window, however, will	Clarifies that patients that experience a second TBI or other severe injury that could interfere with the study during their enrolment should be withdrawn. Also, clarifies that data associated with baseline exams can be collected throughout the study, but is requested/identified at the baseline visit window.

Item	Section	Revision or Clarification	Justification
		be considered a protocol deviation and reported in accordance with Section 9.1. - Management of Protocol Deviations.	
33	Section 7.1. Training Plan for Research Device	**7.2.1 Clinical Site Training ~~on the Research Device~~** **…** **7.2.2 Imaging Laboratory Training ~~on the Research Device~~**	Removed redundant headers to clarify text. There is no change to the intent of these sections.
34	Section 10.1. Foreseeable Adverse Events and Device Effects	Because subjects are having a neurological assessment that includes physical and cognitive tests, there are some risks to subjects completing these assessments. These include physical or mental stress, fatigue, minor to moderate injury risk associated with physical tests (such falls or abrasions during balance tests, in rare cases), and confidentiality risks due to disclosure of personal information (e.g. sociodemographics, health, and occupational status information). The risks associated with these tests are not expected to exceed those encountered during routine examinations of head injury.	Clarifies risks associated with physical and cognitive tests.
35	Section 10.3. Management of Adverse Event Reporting	Any adverse events will be recorded in the subjects study record and the Adverse Event Case Report Form. Subjects will be followed for adverse events and device effects from the time they arrive for each study visit (immediately after providing informed consent for the first visit, and upon arriving to the study area for each subsequent visit, until the subject leaves the study area after each visit). The following information should be obtained:	Clarifies the window for AE reporting in the study.
36	Section 10.4. Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting	All SAEs and or UADEs will be documented as above and reported both electronically and in writing to the Sponsor within 72 hours of knowledge of the event.- The Investigator shall submit the Adverse Event Case Report Form and GEHC_GQP_10.07.005_F002 Site Notification and Assessment of Serious and Unexpected Adverse Events (GEHC internal document DOC0910335) with redacted supporting documentation to SAE mailbox. If the event resulted in the death of a subject, the event shall also be reported via telephone to the Sponsor within 24 hours of knowledge of the event. SAEs will be reported to the local EC/IRB per their policy.	Clarified reporting media for SAEs, in include electronic report.
37	Section APPENDIX E – DATA COLLECTION BY STUDY VISIT	**Note**: The intervals of each visit are defined in Protocol Table 2. Screening for enrollment eligibility should occur before Visit 1 begins, and may be conducted in advance or immediately prior to the start of Visit 1 in accordance with site recruitment practices. Screening and Visit 1 may occur on the same day id the protocol requirements are met. **Visits (Clinical Site)…** **Screening** | **…** **Eligibility**	Added note to clarify screening/recruiting is per local site recruitment procedures. Clarified wording to match revisions in the protocol body.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td ~~Written informed Consent~~</td><td ~~0,1,2~~</td><td>…</td></tr>
<tr><td>Eligibility per the inclusion criteria/ Exclusion criteria</td><td>0,1,2</td><td>…</td></tr>
<tr><td>MR Safety Screening</td><td></td><td>…</td></tr>
<tr><td>Screening completion for eligibility (if applicable)</td><td>1,2</td><td>…</td></tr>
<tr><td>Hamilton Score</td><td>1,2</td><td>…</td></tr>
<tr><td>Zung Score</td><td>1,2</td><td>…</td></tr>
<tr><td>DAST-10</td><td>1,2</td><td>…</td></tr>
<tr><td>AUDIT C [2]</td><td>1,2</td><td>…</td></tr>
<tr><td>Written informed Consent</td><td>0,1,2</td><td>…</td></tr>
<tr><td colspan="3">Baseline medical and demographic data</td></tr>
<tr><td>…</td><td></td><td>…</td></tr>
<tr><td>Certainty of mTBI diagnosis on a 3 point ordinal scale, where 1 = certain mTBI diagnosis, 2 = probable mTBI diagnosis, 3 = possibly mTBI diagnosis) (as defined in Section 6.3.3. Baseline Data Collection: Certainty of Diagnosis)</td><td>1</td><td>…</td></tr>
<tr><td>…</td><td></td><td>…</td></tr>
<tr><td>Site Radiologist Reads of T1, T2, Flair-, ~~and/or SWAN~~and reconstructed SWI and DTI Acquisitions (NINDS TBI CDE Version 4.0)</td><td></td><td>…</td></tr>
<tr><td colspan="3">MR Post-processing (processed at Imaging Laboratory for data from indicated visits)</td></tr>
<tr><td>Post-processing assessment modules and evaluations (Appendix D)</td><td></td><td>…</td></tr>
</table>
</td><td>Added reference to the additional definition of diagnostic certainty provided in the body of the protocol.</td></tr>
<tr><td>38</td><td>APPENDIX D – DETAIL OF POST-PROCESSING ASSESSMENT MODULES</td><td>
Post-Processing Assessment Document Version: 1.0 [Protocol Amendment 4.0]
<table>
<tr><th>Module Number</th><th>Module Title</th><th>Assessments</th><th>Assessor</th><th>Output type</th><th>~~Reader~~ Assessment Instructions</th><th>Type of Stored Files</th></tr>
<tr><td>1</td><td>Volumetry Post-Processing Module</td><td>1. Whole brain
2. Parenchyma
3. Supratentorial region
4. Cortical gray matter
5. Hippocampus
6. Thalamus</td><td>technician (non-radiologist)</td><td>Numerical</td><td>Record the numerical output for each anatomical region as cubic centimeters (cm^3)</td><td>4. DICOM
5. P-files
6. Auxiliary data (if applicable)</td></tr>
</table>
</td><td>Added protocol version number to header. Clarifies that the version found in the protocol is considered the current version until/unless an additional iteration of this page is generated by the Sponsor and signed by the sites.

Removed “Reader” from header to avoid possible</td></tr>
</table>

Item	Section	Revision or Clarification							Justification
				7. Caudate nucleus (labeled as 'Caudate' on device the report) 8. Putamen 9. Globus pallidus (labeled as 'Pallidum' on device report) 10. Amygdala					misinterpretation (as some sites may interpret reader to inherently mean radiologist). Added SWI combination echo post-processing and updated data standards forMR Spect and QSM.
		2	Kurtosis Post-Processing Module	1. ADC 2. eADC 3. FA 4. ParK 5. MuMinK 6. MuMaxK 7. AKC min 8. AKC max 9. Mean K 10. FA-K 11. Color FA	N/A	Twelve (12) electronic quantitative image maps and one (1) corrected diffusion weighted image set	No assessments conducted	4. DICOM 5. P-files 6. Auxiliary data (if applicable)	
		3	RS fMRI Post-Processing Module	1. Default ModePrimary Visual Network 2.Secondary visual 3.Left motor (hand) 4.Right motor (hand) 5.Left motor (face) 6.Right motor (face) 7.Dorsal attention system 8.Executive control network (left) 9.Executive control network (right) 10.Salience network N/A		Thirteen (13) seed-based and thirty (30) ICA-based network images	No assessments conducted	4. DICOM 5. P-files 6. Auxiliary data (if applicable)	
		4	RSI Post-Processing Module	1. free water 2. neurite density	N/A	two (2) electronic quantitative image maps of the brain	No assessments conducted	4. DICOM 5. P-files 6. Auxiliary data (if applicable)	

Item	Section	Revision or Clarification	Justification

5	QSM Post-Processing Module	susceptibility	~~Radiologist or~~ qN/A~~ualified imaging scientist~~	One electronic quantitative image map	~~Check for microbleeds (Microbleeds present Y/N)~~ No assessments conducted ~~Overall IQ (rated as 1 = poor, 2 = some aspects are poor, 3 = acceptable, 4 = good, 5 = excellent)~~	DICOM
6	SWI combined echo	susceptibility	Radiologist	Images	Check for microbleeds (instructions on the reader report form)	4. DICOM 5. P-files 6. Auxiliary data (if applicable)
~~7~~6	MR Spectroscopy	Metabolite ratios	Technician	N/A (numerical values already produced by scanner-based processes)	From the DICOM viewed on AW, record each bilateral value ~~the ratios: NA/Cr, Ch/Cr, mI/Cr and H_2O/Cr. From the text file <pfile>_combine_pro.shf, record the five values(na, cr, ch, mi, h2o) : ratio_val_na, ratio_val_cr, ratio_val_ch, ratio_val_mi, ratio_val_h2o~~	DICOM Text file

APPENDIX H – AMENDMENT TO PROTOCOL VERSION 3.0 TO 4.0

Purpose: This amendment document describes the changes from protocol version 3.0 to 4.0, as follows:

1. To add information for additional study sites and investigators. The listing of sites and investigators is moved to Appendix 1 to conform with current Sponsor requirements.
2. To remove neurological assessments (Stroop Color and Word Test and D-KEFS) to reduce the overall duration (time) of assessments.
3. To add a note that the BESS may be performed in modified form (on a firm surface).

The following amendments were made to version 3.0 to produce version 4.0. Point-by-point revisions are shown as additions in double-underline (double-underline) and deletions in strikethrough (~~strikethrough~~) for each change made in this amendment for the previous version.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td>39</td><td>Study Synopsis / Appendix 1</td><td>[Study site and investigator details are move to Appendix 1]
<table><tr><td>Site 008</td><td>Roland Lee, MD
(Principal Investigator)
Tel: 1 (619) 543-6766
e-mail: rrlee@ucsd.edu</td><td>University of California, San Diego
Radiology/RIL, 9500 Gilman Drive, MC 0852,
La Jolla, CA 92093-0852</td></tr><tr><td>Site 009</td><td>Thomas M. Talavage, PhD
(Principal Investigator)
Tel: 1 (765) 494-5475
e-mail: tmt@purdue.edu</td><td>Purdue University
School of Electrical & Computer Engineering
465 Northwestern Ave
West Lafayette, IN 47907-2035</td></tr><tr><td>Site 010</td><td>Jeffery J. Bazarian, MD, MPH
(Principal Investigator)
Tel: 1 (585) 275-2909
e-mail: Jeff_Bazarian@URMC.Rochester.edu</td><td>University of Rochester Medical Center
Department of Emergency Medicine,
265 Crittenden Blvd,
Box 655C, Rochester,
NY 14642</td></tr></table>[Table Note] * The identifier Site 007 was reserved for a site no longer participating in the study.</td><td>As per current standard documentation requirements of the Sponsor, sites and investigators are placed in an Appendix to the protocol.

Added site and investigator information for additional participating sites (Site 007-009).</td></tr>
<tr><td>40</td><td>Appendix E – Data Collection by Study Visit</td><td><table><tr><td>~~Stroop Color and Word Test~~</td><td></td><td>~~1,2~~</td><td>~~1,2~~</td><td>~~1,2~~</td><td>~~1,2~~</td></tr></table></td><td>Removed neurological assessments (Stroop Color and Word Test) to reduce the overall duration (time) of assessments.</td></tr>
</table>

<table>
<tr>
<td>41</td>
<td></td>
<td>
<table>
<tr><td>~~D-KEFS Verbal Fluency Test (includes Letter Fluency/COWAT test and other primary and secondary measures)~~</td><td></td><td>~~1,2~~</td><td>~~1,2~~</td><td>~~1,2~~</td><td>~~1,2~~</td></tr>
</table>
</td>
<td>Removed neurological assessments (all parts of the D-KEFS) to reduce the overall duration (time) of assessments.</td>
</tr>
<tr>
<td>42</td>
<td></td>
<td>
<table>
<tr><td>BESS [6]</td><td></td><td>1,2</td><td>1,2</td><td>1,2</td><td>1,2</td></tr>
</table>
[Footnote] 6 The BESS should be performed on a firm surface. Foam pads should not be used for BESS testing in this study.
</td>
<td>Added a note that the BESS may be performed in modified form (on a firm surface).</td>
</tr>
</table>

End of Document