GE Healthcare

Clinical Study Protocol:

Clinical Evaluation Of MP26 Features in Adults

(Study No. 114.03-2016-GES-0001)

Version: 4.0; 30/Aug/2016

Sponsor: General Electric Company, acting through its GE Healthcare Business
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Investigational Device/Product: ZTE MRAC and Q Static (Q. MRAC) on the GE SIGNA PET/MR MP software platform

Modality: MRI

FOR QUALIFIED INVESTIGATORS, STUDY STAFF, AND THEIR ETHICS COMMITTEE(S) ONLY

CONFIDENTIALITY STATEMENT

Information in this RESEARCH STUDY PROTOCOL is for investigators, site personnel involved with the study, ethics committee(s), and/or their authorized representative(s) except as required to obtain consent from study participants or as otherwise required by law. Once signed, the terms of the protocol are binding for all parties.

The Sponsor and Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing EC or governing regulatory body, and applicable laws and regulations. The investigator should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Local Principal Investigator at study site:

Investigator Signature	Date
Print Name	
Site Name, Department, Address	

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DOCUMENT AND VERSION CONTROL

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

Revision	Date	Revision Author	Comments/Changes
1.0	17/Jun/2016	Angela Johnson	Clinical writer – initial draft.
2.0	09/Aug/2016	Angela Johnson	Clinical writer – To expand the study population to be inclusive of eligible patients with an indication for PET/CT or PET/MR as detailed in APPENDIX B - AMENDMENT TO PROTOCOL VERSION 1.0 TO 2.0.
3.0	30/Aug/2016	Angela Johnson	Clinical writer – To clarify that subjects will only receive one type of research exam (ZTE or Q.Static) not both, as detailed in APPENDIX C - AMENDMENT TO PROTOCOL VERSION 2.0 TO 3.0.
4.0	30/Aug/2016	Angela Johnson	Clinical writer – Remove legacy element in Table 2 that inadvertently was included in this version when amendment 3.0 was approved in the Sponsor's MWS documentation system.

LIST OF ABBREVIATIONS AND TERMS

3.0T HNU	3.0T Head and neck unit
3.0T LAA	3.0T Lower anterior array
3.0T PET/MR CMA	3.0T PET/MR Central Multiplexed Array
3.0T UAA	3.0T Upper anterior array
8-ChBr	PETMR 8 Channel High Resolution Brain Array
ADE	Adverse Device Effect
AE	Adverse Event
ALARP	As Low as Reasonably Possible
AMA	American Medical Association
CA	Competent Authority
CAPM	GE Clinical Affairs Project Manager
CCG	Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CHF	Clinical History File (synonymous with e-Trial Master File)
CRF	Case Report Form
DCF	Data Clarification Form
EC	Ethics Committee
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice (see ISO 14155:2011) [1]
GE	General Electric
GEHC	General Electric Healthcare
GEMflex coil	GEM (Geometry Embracing Method) Flex Coil Array
ICF	Informed Consent Form
ISO	International Standards Organization
MP	GE MR Program Identifier
MRAC	MR-based attenuation correction
MRDD	Magnetic resonance diagnostic devices
MRI	Magnetic resonance imaging
MWS	GE MyWorkshop Internal Documentation System
PET	Positron Emission Tomography
PET/MR	GE SIGNA hybrid PET and MRI system
PNS	Peripheral nerve stimulation
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Specific Absorption Rate
SNR	Signal to noise ratio
SPR	System Problem Report
T	Tesla
US	United States
ZTE	Zero echo time

STUDY SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is an open label, non-randomized, prospective Clinical research study conducted in a sample population considered representative of the intended clinical population.
Regulatory Status:	This is a pre-market research study of the following devices/products: *Pre-market devices:* Zero echo time (ZTE) sequence for head attenuation correction and Q Static (Q. MRAC) for SIGNA PET/MR MP software platform
Background and Rationale:	The purpose of the study is to collect representative clinical images of demonstrated diagnostic quality using the ZTE MRAC and Q Static (Q. MRAC) on the GE SIGNA PET/MR MP software platform. The images and summary data from this study are intended for use in regulatory submission.
Procedures/ Methods:	Adult subjects with pre-existing clinical indications for PET/CT or PET/MR with radiotracer injection will be enrolled to undergo a PET/MR exam lasting up to 1 hour (which includes screening and approximately 30 minutes of scanning) within the tracer validity time frame in addition to their clinically indicated exam. During each scan, the operator will complete with the ZTE MRAC or Q Static (Q. MRAC) research protocol(s) appropriate for the subject's indication. As part of the study, the corresponding PET/CT images will also be collected for ZTE subjects. Images collected from the sites will be post-processed outside of the clinical care environment by the Sponsor or its delegate using investigational MR post-processing software, and resultant images will be read by the site for diagnostic acceptability and by independent readers for scaled diagnostic image quality, as described in the Blinded Reader Evaluation (BIE) plan. The cumulative results of this study and concurrent studies of the device conducted by the Sponsor may be used to support regulatory submission of the devices under study.
Objectives:	**Primary Objective:** To demonstrate diagnostic image quality of image sets with ZTE MRAC and Q Static (Q. MRAC) for SIGNA PET/MR in representative clinical cases of the general imaging population. **Secondary Objective(s):** To verify diagnostic acceptability, ease of use, and functionality of ZTE MRAC and Q Static (Q. MRAC) for SIGNA PET/MR at clinical sites. **Safety Objective(s):** To collect information about safety events and device issues.
Endpoints:	**Primary Endpoints:** • Independent radiologist/nuclear medicine physician determination of diagnostic image quality considering all evaluable images from each subject (scored on a 5-pt Likert scale) **Secondary Endpoints**: • Site level determination of diagnostic acceptability (Y/N) based on consensus between radiologist(s) and nuclear medicine physician(s) at the site • Ease of use per procedure rated on a 5-pt Likert scale score • Functionality rated for each feature per procedure on a binary (Y/N) performance scale **Safety Endpoints:** Type and number of safety events (AEs and SAEs) and device issues (malfunctions, user errors, and labeling issues) will be summarized.

Summary of Analysis:	The Statistical Analysis Plan (SAP) prepared by the Sponsor's biostatistician prior to the start of independent reading will detail the study analyses.	
Eligibility criteria:	**Inclusion criteria:** Subjects who meet all of the following inclusion criteria may be included that: 1. Are adults (aged 18 or older); 2. Have preexisting clinical indication for PET/CT or PET/MR with radiotracer injection (for subjects that will undergo ZTE procedures, a preexisting clinical indication for PET/CT is required); 3. Are able to undergo PET/MR within the tracer validity time frame after radiotracer injection; 4. Can hear without assistive devices and have necessary mental capacity to follow study instructions; 5. Are willing and able to provide written informed consent; 6. Are considered eligible for MRI and PET exams, according to site institutional safety policies.	**Exclusion criteria:** Subjects who meet any of the following exclusion criteria will be excluded that: 1. Were previously enrolled in the study; 2. If female, are pregnant or of undetermined pregnancy status; 3. Cannot fit safely in the device (>55 cm axial diameter or >227 kgs body weight); 4. Have implants or attached medical devices that could be unsafe for MRI; 5. Have medical conditions or require urgent care that could make it unsafe to participate.
Sample size and Sites:	Up to 75 adult subjects will be enrolled at one site.	
Study duration:	The study is expected to last about 2 months. Estimated start date: 01/Oct/2016 Estimated end date: 01/Dec/2016	

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1. BACKGROUND AND JUSTIFICATION

Hybrid (or combined) PET/MR systems have become available for clinical use in many regions of the world, including Europe, China, and the United States. PET/MR systems combine the capabilities of data acquisition for PET and MR in one device, so that more information can be taken during a single scan session. The excellent functional and morphological MRI capabilities are complemented by the high signal-to-noise ratio PET images. The advantage of this approach is in the possibility of combining the entire range of functional and morphological capabilities of MRI with tracers labeled with radioisotopes that are already commercially distributed, such as 18F-based radiotracers, and other short half-life radioisotopes (e.g. 11C-Choline [2] or 15O-water [3]). This may allow physicians to better highlight specific pathological and physiological mechanisms during clinical exams. PET and MRI are useful for combined diagnostic use to enhance images and indicate cancerous and inflammatory abnormalities in tissues, and contrast-enhanced MR offers potential benefits over routine MR without contrast in identifying revascularization and metastatic movement of cancer. [4, 5, 6]

The planned new release of GE SIGNA PET/MR MP26 software platform introduces several improved features, including Zero echo time (ZTE) scan for head attenuation and Q.Static. Techniques using ZTE MR have been explored for bone visualization and have been shown to be an efficient means of obtaining high-resolution maps of bone tissue with sufficient anatomic accuracy. [7, 8] Images acquired with the ZTE sequence can be segmented to extract bone structure, and this permits anatomically accurate bone to be added to the head attenuation map for attenuation correction of the PET data in PET/MR. [7] Such attenuation correction may be used as an alternative technique to the currently used 'Atlas' method. In addition, the platform will also introduce a Q.MRAC feature, which provides the ability to correct for respiratory motion during the MRAC portion of a PET/MR exam. It has the goal to create a quiescent (end expiratory) phase PET image with a phase-matched MR based attenuation correction, which is intended to provide more accurate attenuation correction for GE Q.Static PET images.

This study is being conducted to demonstrate diagnostic image quality using the ZTE and Q.Static MRAC features in a representative sample of clinical cases requiring head and/or whole-body PET/MR scans.

2. DEVICE/PRODUCT DESCRIPTION

[redacted] Identity, Mechanism, and Function

Name: ZTE MRAC and Q Static (Q. MRAC) on the GE SIGNA PET/MR MP software platform

Modality/Type: MRI

Manufacturer: GE Healthcare

Software version: Correspondent enabling SIGNA software platform

Regulatory Status: Pre-market

The research device(s), instructions for use, or packaging shall indicate that the research device/product is for use in a research investigation, in accordance with US FDA 21 CFR and other applicable laws and regulations. The investigational device will be exclusively used for research purposes.

The results of this study are intended for use in 510(k) submission to the United States Food and Drug Administration (FDA). Results may be used to help commercialize the product in other global regions in the future, at the discretion of the Sponsor.

[redacted] Zero echo time (ZTE) Software Feature

The GE SIGNA PET/MR MP26 software platform includes the zero echo time (ZTE) scan for head attenuation and Q.Static. The ZTE MR software feature has the potential to enable better visualization of bones, including those in the head, by employing optimal head attenuation correction in PET/MR. ZTE functions serves a similar clinical purpose as existent visualization techniques (for example Atlas scans).

[redacted] Q Static (Q. MRAC) Software Feature

In addition, the platform will introduce an improved Q.Static feature with Q. MRAC, where phase matching the MRAC with the quiescent phase is employed to get more accurate attenuation correction for our Q.Static PET images. The planned new release of GE SIGNA PET/MR MP26 software platform introduces an improved Q.Static feature with Q.MRAC, which provides the ability to correct for respiratory motion during the MRAC portion of a PET/MR exam. It has the goal to create a quiescent (end expiratory) phase PET image with a phase-matched MR based attenuation correction, which is intended to provide more accurate attenuation correction for GE Q.Static PET images.

[redacted] Intended Use

ZTE MRAC and Q Static (Q. MRAC) on the GE SIGNA PET/MR MP software platform are MR features intended to be used by trained physicians to aid in diagnosis. The procedures conducted in this study are intended for research purposes and are not intended as a substitute for required medical care.

[redacted] Concomitant/Ancillary Administrations

[redacted] Medications and Biologic Products

No medications or biologic products will be administered as part of the study procedures. Prior to participation in the study, subjects with clinical indications for PET/CT or PET/MR exams will receive their clinically indicated injected radiotracer and any other medically necessary medications as ordered by their regular physician. Due to the in vivo half-life of radiotracer agents, it is reasonably expected that

subjects participating in the study will have active radiotracer in their bodies during their additional research PET/MR scan; therefore no additional radiotracers will be administered as part of the study. No sedatives or contrast agents will be administered for research purposes.

[redacted] Dosimetry

It is important to note that the patient will not receive a second radiotracer injection for the research PET/MR study. The residual radioactivity from the initial radiotracer injection of the clinical PET exam will be adequate.

[redacted] Laboratory Tests

No laboratory tests are planned as part of the study procedures.

[redacted] Accountability

Accurate and adequate records will be maintained for all devices, from time of shipment to the sites until return or disposal of all devices issued by the Sponsor as part of this study, as required by applicable laws and regulations. The Principal Investigator will be ultimately responsible for the security and integrity of research devices/products at the investigational site during the course of the study. The unique identifying information of post-processing devices used as part of this study will be recorded by the Sponsor.

[redacted] Issuance

The investigational PET/MR software will be provided by Sponsor and installed on existing hardware platforms installed at the investigational site. Some parts of the study require post-processing of clinically acquired MR data conducted outside of the clinical care environment. Study post-processing will be conducted under the control of the Sponsor and may utilize investigational software and workstations required for post-processing tasks (such as AW Workstations or equivalent). No human subjects will be directly exposed to post-processing devices as part of this study. The Sponsor will provide necessary installation support, calibration, and maintenance to the device and its software components as necessary to ensure safety and maintain integrity of study data.

[redacted] Disposition

The investigational components provided by the Sponsor will be uninstalled after the study by this Sponsor, in accordance with applicable laws and regulations. Identifiable subject information will be removed from devices, including post-processing software and workstations, used by or returned to the Sponsor at the end of the study.

[redacted] Anticipated Risks and Benefits

The devices under study have undergone risk assessment, in accordance with International Standards Organization (ISO) 14971:2010, and risks have been mitigated to levels as low as reasonably possible (ALARP). Risks associated with the PET/MR procedures in this study are similar to the risks found in typical clinical MR (field strengths less than 3.0T) or PET scans using devices that are already approved for regular commercial use. Hybrid (combined) PET/MR systems have been commercially available in the Europe and the US since 2011, and the GE PET/MR SIGNA system has been commercially marketed in 2015 in the US and EU.[7, 8] During a typical PET/MR exam, patients will be exposed to minimal levels of

ionizing radiation from their clinically indicated PET radiotracer administration and the magnetic and electromagnetic fields of the device, at levels within the ranges set forth by established safety standards. [9]

The study does not require any clinical follow-up. There are no expected risks to subjects, operators, or others in this study beyond those of comparable clinical diagnostic imaging procedures routinely used in clinical practice. Subjects are not expected to benefit directly from study participation. The results may benefit future patients by helping to better understand new technology to support PET/MR technology development and commercialization.

[redacted] Risk Category and Rationale

The ZTE MRAC and Q Static (Q. MRAC) on the GE SIGNA PET/MR MP software platform and associated MR hardware and software systems required for this research, as used in this study, are not considered a significant risk device per the 21 CFR §812.3 definition:

1) it 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) it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

In the United States (US), the SIGNA PET/MR Scanners (GE Medical Systems, LLC, Waukesha, WI) is considered Class II magnetic resonance diagnostic devices per 21 CFR §892.1000. In the US, MR software features under study are considered pre-market MR software components under 21 CFR §892.1000 and Class II Picture archiving and communications system per 21 CFR §892.2050. Workstations for processing MR images (such as the VolumeShare Advantage 5 or “AW”) are considered to be a Class II Picture archiving and communications system per 21 CFR §892.2050.

3. STUDY OBJECTIVES AND ENDPOINTS

[redacted] Purpose of the Study

The purpose of the study is to collect representative clinical images with demonstrated diagnostic image quality using ZTE MRAC and Q Static (Q. MRAC) software features. The images and summary data from this study are intended for use in regulatory submission(s).

[redacted] Primary Objective:

To demonstrate diagnostic image quality of image sets with ZTE MRAC and Q Static (Q. MRAC) for SIGNA PET/MR in representative clinical cases of the general imaging population.

[redacted] Secondary Objective(s):

To verify diagnostic acceptability, ease of use, and functionality of ZTE MRAC and Q Static (Q. MRAC) for SIGNA PET/MR at clinical sites.

[redacted] Safety Objective(s):

To collect information about safety events and device issues.

[redacted] Study Endpoints

[redacted] Primary Endpoints:

Independent radiologist/nuclear medicine physician determination of diagnostic image quality considering all evaluable images from each subject (scored on a 5-pt Likert scale)

[redacted] Secondary Endpoints:

Site level determination of diagnostic acceptability (Y/N) based on consensus between radiologist(s) and nuclear medicine physician(s) at the site

Ease of use per procedure rated on a 5-pt Likert scale score

Functionality rated for each feature per procedure on a binary (Y/N) performance scale

[redacted] Safety Endpoints

Type and number of safety events (AEs and SAEs) and device issues (malfunctions, user errors, and labeling issues) will be summarized.

[redacted] Summary of Study Design

This is a pre-market, open label, prospective, non-randomized clinical research study at one site. The study is designed to allow for sample PET/MR image collection and to demonstrate diagnostic image quality of resultant sample image sets from each participating subject. The results of this study will be analyzed according to a prospective Blinded Image Evaluation (BIE) plan and Statistical Analysis Plan (SAP) prepared by the Sponsor prior to the start of image reads. This study is run concurrently with other studies of the device conducted by the Sponsor and it is prospectively expected that the cumulative results of these studies may be used to support regulatory submissions.

4. STUDY DESIGN

[redacted] Study Population

Subjects will be enrolled that have a clinical indication for PET/CT or PET/MR with radiotracer injection prescribed for their medical care outside of the study. Sites should make reasonable attempts to ensure diversity of clinical state (including injury severity or extent of disease progression) within the enrolled population in order to achieve a sample maximally representative of the intended use population.

[redacted] Number of Subjects

The study aims to acquire up to 75 clinical PET/MR image sets (up to 38 subjects will be enrolled to have a ZTE MRAC exam and the remaining 37 subjects will be enrolled to have a Q Static (Q. MRAC) exam. In the event that a subject scan does not produce images, as in the case of withdrawal or technical issues preventing scanning, additional subjects may be enrolled until the target number is achieved (not to exceed a maximum of 75 subjects during the course of the study) as described in Section 10.2 - Sample Size Determination. The minimum number of necessary subjects will be enrolled to achieve the target number of datasets.

[redacted] Enrollment Quota

Subjects will be enrolled based on a quota block method based on scan type (relative to the patient clinical indication for PET/CT or PET/MR). Each subject may have only one type of scan towards these quota blocks (ZTE or Q.Static MRAC), not both (Table 1).

Table 1. Target quota blocks for subject enrollment/target datasets

Scan Type	**Target number of subject datasets (N_{Target} = 30)**
ZTE MRAC	At least 30 subject scans (N_{neuro} = 30 to 38)
Q Static (Q. MRAC)	At least 30 subject scans (N_{body} = 30 to 37)

[redacted] Protection of Vulnerable Subjects

Vulnerable subjects are individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s), or other parties participating in, or contributing to, the clinical investigation.

All investigators shall avoid improper influence on, or inducement of, the subject, Sponsor, monitor, other investigator(s), or other parties participating in, or contributing to, the clinical investigation.

This study does not examine any groups of subjects who are considered to be vulnerable subjects in the country in which the study is being conducted.

[redacted] Eligibility Criteria

[redacted] Inclusion Criteria

Subjects should be recruited to cover a variety of clinical indications which represent clinical cases seen in PET examinations. Subject must meet all of the following inclusion criteria to be included:

1. Are adults (aged 18 or older);
2. Have preexisting clinical indication for PET/CT or PET/MR with radiotracer injection (for subjects that will undergo ZTE procedures, a preexisting clinical indication for PET/CT is required);
3. Are able to undergo PET/MR within the tracer validity time frame after radiotracer injection;
4. Can hear without assistive devices and have necessary mental capacity to follow study instructions;
5. Are willing and able to provide written informed consent;
6. Are considered eligible for MRI and PET exams, according to site institutional safety policies.

[redacted] Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded that:

1. Were previously enrolled in the study;
2. If female, are pregnant or of undetermined pregnancy status;
3. Cannot fit safely in the device (>55 cm axial diameter or >227 kgs body weight); [1]
4. Have implants or attached medical devices that could be unsafe for MRI; [2]
5. Have medical conditions or require urgent care that could make it unsafe to participate

[1] The **maximum patient size for the bore** is an axial diameter of 55 cm (~21.7 in.) or weight of 227 kgs (~500.5 lbs).
[2] Potentially unsafe devices include metallic/conductive or electrically/magnetically active implants or attached medical devices (except dental devices/fillings, surgical clips, and surgical staples), as determined by the site institutional MRI safety policies.

[redacted] Recruiting and Screening

Subjects will be recruited for potential enrollment in this study prior to their clinically indicated PET/CT or PET/MR exam according to the institutional procedures of the investigational site and its governing IRB. Participants identified after completing their clinically indicated imaging exam may be recruited, if otherwise eligible and within the study time window. All participation will be voluntary, and written informed consent will be collected from each participant prior to exposure to any investigational devices or procedures.

Subjects will be screened for enrollment in this study against the inclusion and exclusion criteria according to the standard procedures of the investigational site.

Following recruitment, a subject will be considered enrolled (the point of enrollment) once he/she signs and dates the informed consent form (ICF). Safety events and device issues will, however, only be reported during the period of exposure to the investigational PET/MR device (from the time the subject enters until the time the subject leaves the PET/MR suite), and not for clinically indicated imaging (e.g. PET/MR or PET/CT) procedures that may be observed after the patient provides consent but are not a consequence of study participation.

Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject. The unique subject number will be used to label case report form (CRF) data for the subject throughout his/her participation in the study.

[redacted] Criteria for Withdrawal/Discontinuation

A subject may withdraw from study participation at any time, for any reason. The investigator may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor. The EC should be notified per their notification of subject withdrawal policy.

5. STUDY PROCEDURES

[redacted] Activities Prior to Research PET/MR Exam

For all subjects, study staff will confirm that the subject is eligible and complies with applicable site requirements prior to starting study procedures. After the subject completes the ICF, he/she will be required to complete certain activities to participate in the study.

[redacted] Pre-Screening Activities (All Subjects)

- **Verify site institutional policy(ies) for MR safety are followed**.
- **Record implant information** for subjects with implants allowable per the inclusion/exclusion that will be present during scanning (with the exception of passive dental filling/implants, surgical clips, or surgical staples)*, as follows:
  i. Name of the device
  ii. Manufacturer of the device
  iii. Model Number of the device

  ***Note**: If any or all information is not available, write N/A in the applicable area(s)*
- **Record subject characteristics**, as follows:
  i. age (in years)
  ii. gender
  iii. weight
  iv. height

[redacted] Pre-Screen Activities for PET/CT Subjects

- **Record clinically indicated PET/CT information** (before the PET/CT scan when possible to limit delay time between PET/CT and research PET/MR exam), including start and end time of the PET/CT scan and information about injected radiotracer, as follows:
  i. radiotracer type, dose and units, and time of injection
  ii. clinical indication for PET/CT scanning (oncology, neurology, and/or cardiac etc.)
  iii. date and time of PET/CT
- **Check for completeness** of acquired PET/CT images, if a subject is missing required PET/CT images, the subject may be withdrawn from the study. PET/CT images will be collected as part of the study.
- **Check for solid food or insulin administration**. If a study subject is administered insulin, solid food, or any non-water beverage prior to the PET/MR imaging that can be expected to interfere with radiotracer activity, the subject may be withdrawn from the study at the discretion of the investigator if such administration(s) could interference with performing study procedures and/or radiotracer bioavailability during the study period.

[redacted] Activities Required before Study PET/MR for All Subjects

- **Encourage subjects to empty their bladder** prior to PET/MR scanning.
- **Provide MR-safe clothing** according to participating investigational site's standard procedures, such as hospitals gowns, and isolate all non-MR compatible equipment or devices and route the devices and/or cables as required out of the magnet room.

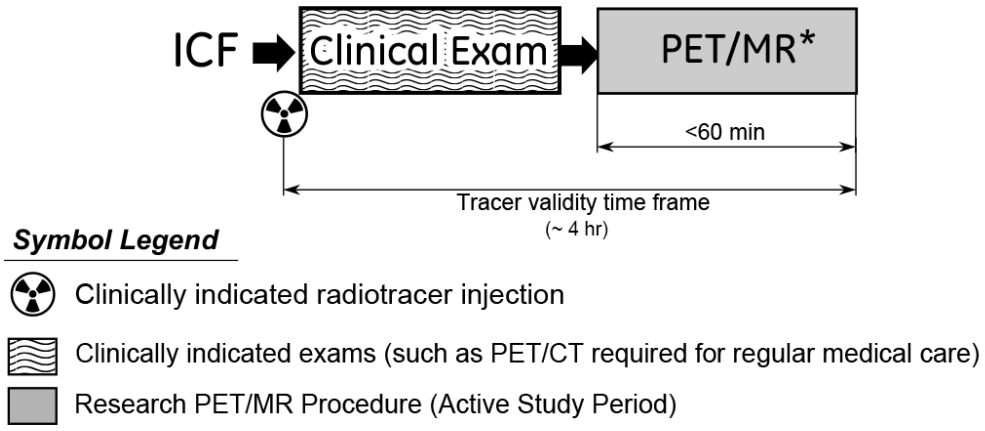
- **Provide mandatory hearing protection**, as per site institutional procedure.

[redacted] Activities during Research PET/MR Scanning and Data Acquisition

[redacted] Subject Procedure

The site should perform research PET/MR scans during the time that the radiotracer validity time frame. Typically research PET/MR exams should be started with approximately 4 hours of radiotracer administration; however, the site may scan a subject at their discretion is the scan is expected to take place during the clinical validity window based on the investigator's expertise (not required to be within 4 hours, Fig. 1). This is to ensure sufficient radiotracer activity during the investigational procedure.

Figure 1. Study procedure for research PET/MR scans relative to clinically indicated imaging (PET/CT or PET/MR) with injected radiotracer



*MR Safety Screening and Pre-screening activities identified in Section 5.1 Activities Prior to PET/MR (Pre-Screen) should be completed prior to the start of the study PET/MR scan.

The research PET/MR scan session will be performed while the subject is lying on a scan table. During this time, the subject may be asked to shift position to one side or another, lie still and to follow simple instructions such as to hold his/her breath at specified times. Subjects may be provided with a calling system that allows him or her to contact the Device Operator at any time during the scan. While the subject is in the scanner, the device operator will remain where the subject is visible (e.g. through a window) and audible (e.g. through an intercom).

The PET/MR exam may last up to a 1 hour (which includes screening and approximately 30 minutes of scanning). Start and end time of research PET/MR scanning and additional information will be recorded as per Table 2.

[redacted] ZTE MRAC and Q Static (Q. MRAC) PET/MR Scanning Procedure

The device operator will acquire scan data using default PET/MR scan protocols, default MR-only scan protocols, and other scanning protocols optimized by the operator as appropriate for the subject's clinical state. The scan protocols and associated pulse sequences used shall be chosen by the investigator. For PET/MR simultaneous scanning, the first scan will be a whole body localizer. The user will then define n beds ($n \leq 14$). The user will have the option to insert as many MR scans at each bed position, although a MR attenuation correction scan will always be acquired first at each bed position (approximately a 30 second scan). The PET will continue to acquire data until the time set by the

operator has elapsed. The system will then automatically move to the next bed position. The user will be able to view the PET images overlaid on the MR images from each bed after it has been reconstructed.

During each scan, the operator should complete ZTE MRAC or Q Static (Q. MRAC) protocol appropriate for the subject's indication, and record the sequence used in the exam. For Q Static (Q. MRAC) scans, the site should conduct 5 non-gated MRAC acquisitions and 5 gated acquisitions for each subject around the lung/abdominal region including the diaphragm. For all scans, the device operator should attempt to complete both PET and MRI scans on the PET/MR system and to collect an image set that includes both PET and MRI images. At the end of each scan session, the device operator will record information about the device used, the time of the scan session and his/her observations in the Case Report Forms (CRFs). If the device operator is unable to collect both PET and MRI images, he or she should record the reason on the Case Report Form (CRF). The device operator will save the images and raw data.

Table 2. Characteristics recorded to the CRF during PET/MR scan sessions

Coil(s) Used	Gating device(s) used	Medical tubes wires/cables
• 3.0T PET/MR CMA • 3.0T HNU • 3.0T UAA • 3.0T LAA • GEM Flex Coil 16-S, M, L Array • 3.0T Split head coil • PETMR 8Ch HiRes Brain Array • 3.0T HD Flat GEM Table Breast Array • Other, specify	• Respiratory bellows • ECG leads • Peripheral gating photopulse sensor	• None • IV • Catheterization • Breathing tube • Oxygen • ECG Monitor • Other, specify

[redacted] Emergency Procedures

In the event of a medical emergency, the scan will be stopped immediately and facility's emergency response plan will be followed. The subject will be provided with emergency care as needed.

The subject's care shall take precedence over any imaging associated with the study. In the event the subject experiences discomfort or wishes to stop the exam for any reason, the exam will be immediately stopped and appropriate follow up response will occur. The event will be recorded in compliance with US FDA and GE Healthcare safety reporting requirements.

[redacted] Incidental Findings

The additional PET/MR procedures performed in this study are for research only and are not intended for diagnostic use. Should the device operator observe what they interpret to be a potential abnormality, the investigator will evaluate the findings and alert the patient if necessary. The investigator may recommend diagnostic exams to be performed independent of the study. No medical or diagnostic care of any kind will be rendered based on study image sets using the research PET/MR.

[redacted] Activities after PET/MR Scanning

Upon completion of the exam, the device operator or those assisting him/her will assist the subject from the device and out of the scan area. Any reported safety or device issues will be recorded to the CRF up until the time the subject leaves the PET/MR suite.

After the exam is complete and the subject has left the PET/MR suite, the device operator will complete the CRF and store the image sets for the scan, which will be labeled with the subject's unique ID number. All images collected from clinical sites will be sent to the Sponsor or its delegate for investigational post-processing with the investigational technology prior to image reads.

[redacted] Follow-up Visits

All patient procedures will be conducted during a single visit. No follow-up visits are required.

6. STUDY DATA COLLECTION AND ASSESSMENTS

[redacted] Primary Assessment

[redacted] Independent Reader Determination of Diagnostic Image Quality

Diagnostic image quality will be rated on a 5-pt Likert scale by at least 2 independent board certified nuclear medicine physician and/or radiologists for all evaluable image sets (including all clinically acquired MR image sets able to be successfully post-processed that are complete image sets [not from cases of withdrawal or critical deviation that could impair to the quality of data]). Independent reads will be conducted outside of the clinical care environment according to the procedures specified in the Blinded Image Evaluation (BIE) plan prepared by the Sponsor prior to the start of image reading. Identifiable subject information will be removed prior to independent reads.

Diagnostic image quality will be recorded on a 5-pt Likert scale, where ratings of ≥3 are considered acceptable for diagnostic use and ratings of 1-2 are considered unacceptable for diagnostic use, as follows:

1. **Unacceptable** (cannot be used for diagnostic use)
2. **Poor** (not completely suitable for diagnostic use)
3. **Acceptable** (suitable for diagnostic use but with minor defects)
4. **Good** (good suitability for diagnostic use)
5. **Excellent** (excellent suitability for diagnostic use)

The reader should record the rationale for any image scored unacceptable for diagnostic use (scores of 1 or 2). And/or provide comments in image annotation or point to the problem area in the images. Scores should be based on the entire image set, considering all available views, with the exception of the LAVA sequence used for MR-attenuation correction (which should not be considered in the evaluation for image quality).

[redacted] Secondary Assessments

[redacted] Site Determination of Diagnostic Acceptability

Based on consensus of at least one radiologist and at least one nuclear medicine physician at the site, diagnostic acceptability of each evaluable image set (including all clinically acquired MR image sets able to be successfully post-processed that are complete image sets [not from cases of withdrawal or critical deviation that could impair to the quality of data]).

Binary diagnostic image quality will be recorded by the site on a single CRF that includes the names and signatures of both the radiologist and nuclear medicine physician making the evaluation, as follows:

"**Is the image of acceptable quality for diagnostic use? (Y/N)"**

The reader should record the rationale for any "no" answer indicating that the image is not acceptable quality for diagnostic use. And/or provide comments in image annotation or point to the problem area in the images. Scores should be based on all views included in the image set, considering all available views, with the exception of the LAVA sequence used for MR-attenuation correction (which should not be considered in the evaluation for image quality).

[redacted] Ease of use

Each of the following ***ease of use*** parameters will be rated by the device operator on a 5-point scale (1 = challenging, 2 = somewhat challenging, 3 = neutral neither challenging nor easy, 4 = somewhat easy, 5 = easy), where scores of ≥3 are acceptable, as follows:

- Prescribing and Scanning
  - Prescribing PET scan
  - Prescribing MR scans simultaneous with PET
  - Starting and monitoring scanning
  - Reviewing PET and MR image sets
- General Workflow
  - Overall process of doing this exam
  - Performing exam within acceptable duration to meet normal site workflow requirements

[redacted] Functionality

Each of the following parameters for ***functionality*** will be rated by the device operator on a binary (Y/N) scale, as follows:

- Did the system function to view the PET, MR, and/or fused image sets?
- Did the system function to position subject and coils in scanner?
- Did the system function to prescribe and scan this exam? If no, indicate which (PET, MR, and/or fused did not function properly).

If no is indicated for any functionality, the investigator should indicate the reason in a provided area for comments on the Case Report Form (CRF).

[redacted] Safety Assessments

The description, severity, and device relatedness of any AE or SAE during the study will be recorded. Subjects will, if necessary, be provided with emergency care. In the event of any device issues, the event will be recorded. Safety reporting will be conducted as described in this protocol.

7. QUALIFICATION AND TRAINING PLAN

[redacted] Staff Qualifications

All members of the study staff participating in the conduct of the investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per US FDA and ISO 14155:2011.

[redacted] Reader Qualifications

All readers in this study will:

- Have >4 years of direct experience in evaluating MRI and/or PET image sets.
- Be certified as diagnostic radiology and/or nuclear medicine physicians.

[redacted] Training Plan for the Protocol and Research Device/Product

Before starting the study, the study staff will be trained on the clinical investigation requirements set forth in this study protocol according to the study *Training Plan* stored in the Sponsor's Clinical History File (CHF).

Study staff directly operating or maintaining the investigational PET/MR system will be trained based on the training plan and device documentation. Device operators will be qualified to operate the devices, as per the policies of the site.

The Principal Investigator will be ultimately responsible for execution of this study in accordance with the protocol and for devices used in this study by members of the study staff.

8. SAFETY

[redacted] Anticipated Adverse Events

MR technologies up to 3.0T have been used in clinical applications for over 30 years and have a well-documented safety profile. Similarly, PET scanners are widely used in clinical practice. The PET/MR scanner does not involve any risks other than those normally associated with routine clinical PET and MRI scans, similar to those already performed in many hospitals. The following are some discomfort one may experience during a PET/MR scan session.

Movement of metal objects: PET/MR systems operate in a high field magnetic field typical of MRI systems, which can cause movement or projectile motion of certain ferrous metal objects. Though injuries are rare (occurring in less than one of 100,000 patients), small objects can cause bruises or cuts, and large objects can cause severe trauma or even death.

Implants: Objects embedded within the body can be affected by the strong external magnetic field near and inside of the PET/MR device during an MRI exam, causing movement and/or electronic malfunction that can lead to injury or even death.

Warming and burns: Radiofrequency (RF) energy transmitted by the PET/MR system during MRI scanning can result in generalized or localized heating of body tissues, occurring in about 5-10% of

patients. Some subjects may experience sensations of warming and/or perspiration, which can be uncomfortable. Though warming can cause burns, severe injuries are rare.

Peripheral nerve stimulation (PNS): During a PET/MR exam, rapidly changing magnetic fields during MRI exams can cause stimulation of nerves, causing unusual generalized or localized "tingling" sensations, known as peripheral nerve stimulation (PNS). PNS normally occurs in 5-10% of subjects, but may occur in up to 50% of subjects under certain conditions.

Acoustic Noise: During PET/MR, the MRI system is capable of generating acoustic noise levels higher than 99dB. The acoustic noise levels of the system do not exceed 140 dB under worst-case conditions. Sometimes, transient hearing loss or "ringing" in the ears (tinnitus) can occur, which it typically is mild and resolves spontaneously after scanning. Severe or chronic hearing conditions can occur if proper hearing protection is not used, but are rare (occurring in less than one of in 100,000 patients).

PET Radiotracers and MR contrast agents: Subjects in this study will be administered PET radiotracers prescribed as part of their normal medical care, and dosage will not be changed or increased by participating in this study. Though no MR contrast agents are being administered solely for the purposes of this study, some patients may have incidentally received MR contrast as part of regular medical care prior to starting study procedures. The safety and risk profiles of PET radiotracers and MR contrast agents are well documented and are not increased by having a PET/MR scanning. These risks vary by the type of agent administered, but most commonly include:

- warm or hot ("flushed") sensations that typically resolve spontaneously;
- transient "metallic" taste that typically resolves spontaneously;
- allergic reactions, ranging from mild irritation, such as itching and hives that may resolve spontaneously, to a life-threatening emergency (anaphylactic reaction) that requires additional medical care;
- kidney damage as the agent is excreted from the body, a potentially severe condition called nephrotoxicity. Risk is increased for subjects with diabetes, chronic renal disease, advanced congestive heart failure, concomitant use of non-steroidal anti-inflammatory agents (NSAID).
- unintentional penetration of agents into the local areas surrounding tissues, either by leakage (e.g., because of brittle veins in very elderly patients) or direct exposure (e.g. because the needle has punctured the vein and the infusion goes directly into the arm tissue), a condition known as extravasation. Extravasation typically causes mild effects, such as pain, reddening, or irritation at the injection site, but can, in rare cases, cause severe injury requiring medical care.
- for PET radiotracers, a radioactive drug (radiotracer) is injected into the body. This results in a small amount of radiation exposure, at very low levels not typically associated with any adverse effects on the body.
- for gadolinium-based MR contrast agents, a rare and serious side effect of contrast administration is formation of fibrotic nodules and indurations on the skin and other tissues throughout the body, called nephrogenic systemic fibrosis (NSF), which is painful and typically requires additional medical care.

Due to possible effects in the developing fetus and health of the mother, no women that are pregnant or suspected to be pregnant will be included in this study.

There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.

[redacted] Adverse Event Definitions

Adverse Event (AE): 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 [ISO 14155:2011 3.2]. This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons, this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): an adverse event that led to death; led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE [ISO 14155:2011 3.37].

Adverse Device Effect (ADE): an adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].

Serious Adverse Device Effect (SADE): an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].

Device deficiency: an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].

Unanticipated serious adverse device effect (USADE): a serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report [ISO 14155:2011 3.42]. In the United States, 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 study documents, will be reported in accordance with 21 CFR §812.3 and applicable laws and regulations.

[redacted] Documentation of Safety Events

All adverse events (AE), including all serious adverse events (SAE), are required to be collected, investigated, and documented during the study reporting period, as defined in the study procedure as the time the subject enters until the time the subject leaves the PET/MR suite. Documentation will include:

- Description of Event

- Date of onset and resolution
- Severity (mild, moderate, or 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)
- Causal relationship to investigational medical device? (not related, possibly related, or related)
    - *Not related*: 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.
    - *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, or no action)
- Anticipated (yes/no): Anticipated adverse events for this study are defined in Section Anticipated Adverse Events.

Reporting of Safety Events and Device Deficiencies/Complaints

The following events are to be reported to the Sponsor within 72 hours of the event occurrence and to the EC per their policy:

- All SAEs and USADEs
- All device issues that could possible lead to an SAE

Any study-related death should be reported to the Sponsor with 24 hours. Additional follow-up information may be requested by the Sponsor. In addition, safety information may be shared with regulatory agencies and other participating sites, as required by applicable law and regulation.

Device Deficiencies/Complaints

Device deficiencies/complaints should be reported to the study Sponsor contact identified on the cover page of this protocol. All device deficiencies/complaints will to be collected, fully investigated, and documented in the source document and appropriate case report form (CRF) during the study reporting period. The Principal Investigator is responsible for notifying the Sponsor in the event that there is any device issue that could potentially lead to a SAE.

9. ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of Good Clinical Practice (GCP) for medical devices, as set forth by ISO 14155:2011 and ISO 14971:2010; applicable sections of US FDA 21 Code of Federal Regulations (CFR); and any other applicable state or national legal requirements in the United States.

The study will be conducted and reported in accordance with applicable policies of the requirements of the Ethics Committee (EC) and governing regulatory authorities.

If national or regional EC requirements are less strict than the requirements of GCP, such as ISO 14155:2011 for medical devices, the Sponsor shall apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

[redacted] Ethics Committee

The responsible Principal Investigator at each site will ensure that approval from an appropriately constituted EC is attained for the clinical study prior to enrolling subjects, and Principal Investigator will ensure that documentation of approval is maintained for the duration of the study.

The Principal Investigator will ensure that the Sponsor is notified of any withdrawal of EC approval within 5 working days of such occurrence. If approval is terminated or suspended, the Principal Investigator will promptly notify the Sponsor and provide written explanation.

[redacted] Regulatory Agencies and Competent Authority(ies)

This study will be conducted in accordance with US FDA requirements. Registration with the agency prior to the start of the study is not required for this image evaluation study, in accordance with applicable laws and regulations. Any additional requirements imposed by the EC or regulatory authority shall be followed.

[redacted] Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the EC.

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and wellbeing of human subjects may proceed without prior approval of the Sponsor and the EC/competent authority (CA). Such deviations shall be documented and reported to the Sponsor and the EC as soon as possible. Deviations will be reported as:

- **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 per the deviation reporting policy.
- **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 CRF Protocol Deviation page and will be reviewed by the study monitor.

Non-substantial modifications may be made during the normal course of device optimization, maintenance, and feasibility testing. Non-substantial modifications will be communicated to the CA as soon as possible, if applicable, and to the EC per their policy.

[redacted] Participant Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational device (if applicable), the potential risks and benefits, and any potential discomforts. Each participant will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for the study will be provided an ICF, describing the study and providing sufficient information to allow the participant to make an informed decision about his/her participation in the study. Informed consent documents will be subject to approval by the EC prior to enrolling subjects in the study.

The participant should read and consider the statement before signing and dating the ICF, and shall be given a copy of the signed document. The ICF must also be signed and dated by the investigator (or his/her designee), and it shall be retained as part of the study records.

[redacted] Early Termination of the Study

The Sponsor may terminate the study prematurely according to certain circumstances. Examples of such circumstances include ethical concerns, insufficient participant recruitment, participant safety concerns, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, early evidence of benefit or harm of the research product, or for any other reason.

10. STATISTICAL METHODS

[redacted] Statistical Hypothesis

No statistical hypothesis is being prospectively tested in this study. As necessary for regulatory submission, additional analyses will be detailed prior to the star to independent reads in the Statistical Analysis Plan (SAP) prepared by the Sponsor's biostatistician.

[redacted] Sample Size Determination

The sample size is based on the Sponsor's engineering determinations of the required number of sample images, and is not prospectively powered to produce statistically powered results. The protocol aims to acquire 30 images using Q Static (Q. MRAC) and 30 images using ZTE. Datasets may include one or both image type, based on clinical availability, to meet these targets. Assuming than 10% of cases will include both types of data and 25% attrition rate due to various causes, this study requires a population (*N*) such as that:

$$1.1N - (1.10 \times N)(0.25) = 30\ ZTE + 30\ Q\ static$$

To satisfy this requirement, a minimum population size of *N = 72* is required. This is approximated to *N* = 75, as this number is considered by the Sponsor to be sufficient to account for unforeseen contributions to dropout or evaluable image rates.

[redacted] Statistical Analysis

[redacted] General Statistical Methods

The study data will be presented in tables, listings, and figures. Data will be summarized using descriptive statistics. The descriptive statistics for variables will include mean, standard deviation, median, Q1 and Q3, minimum, maximum, and count. Categorical variables will be described with counts, percentages. If necessary for regulatory submission, additional statistical methods may be employed as detailed in the Statistical Analysis Plan (SAP) prepared by the Sponsor's responsible biostatistician and stored in the study's clinical history file (CHF).

[redacted] Analysis Set(s)

The study analysis sets include the Safety Population and Per-protocol population.

The safety population includes all subjects enrolled and scanned, the per-protocol population include all subjects enrolled, scanned, processed with ZTE and/or Q-static and without critical protocol deviation.

[redacted] Analysis of Primary Endpoint(s)

General descriptive statistical methods will be used to summarize the study diagnostic image quality results by reader and overall.

[redacted] Analysis of Secondary Endpoint(s)

General descriptive statistical methods will be used to summarize each secondary endpoint.

[redacted] Safety Analysis

Tables and listings of safety events, deviations, and device issues will be prepared, including counts and percentages as appropriate.

10.3 Interim Analysis

No interim analyses are prospectively planned as part of this study.

[redacted] Handling of Missing Data

Analysis will be based on collected data, and no imputation will be done for missing data.

[redacted] Deviation(s) from the Original Statistical Plan

Any changes or deviations from the original statistical plan specified in this protocol will be described and justified in the SAP and/or study final report as required by ISO 14155:2011.

11. QUALITY ASSURANCE AND CONTROL

[redacted] Data Management

Data management processes for handling study data will be maintained by the Sponsor.

[redacted] Completion of Case Report Forms (CRFs)

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents. Paper CRFs and/or electronic CRFs (eCRFs) will be used to collect data. The Sponsor will provide CRFs and train study staff on completion of CRFs using Good Documentation Practices (GDP). CRF Completion Guidelines (CCG) may be provided by the Sponsor to help facilitate training.

CRFs are to be completed as information becomes available at the site. CRFs should be signed by indicated parties, in indicated area(s), to certify the contents of the form. The Principal Investigator is ultimately responsible for ensuring completion of CRFs.

If discrepancies are discovered on paper CRFs during monitoring, the Sponsor's representative will ensure that the study staff makes necessary corrections directly to the CRF(s) prior to collection.

Following CRF collection, the Sponsor will review the data. A Data Clarification Form (DCF) may be provided to the site to correct or clarify discrepancies.

If a site discovers discrepancies after CRF collection, the site may notify the Sponsor and request data modification.

[redacted] Data Handling and Record Keeping

All documents and data shall be produced and maintained in a manner that assures control and traceability.

[redacted] Source Data and Documents

Source data includes information in original records, certified copies of original records of clinical findings, observations, or other activities for the study. Source documents for each subject must be retained throughout the investigation, including printed or electronic documents containing source data. Elements should include:

- **Source data and documentation** relevant to data recorded for subject screening and CRF corroboration.
- **Subject records** containing the completed ICFs and CRFs
- **Regulatory binder** containing the protocol and any subsequent amendments, EC submissions and approvals, blank ICF(s), and site logs
- **Reference manuals** containing investigator responsibilities, Sponsor, AE/SAE and informed consent guidelines, applicable study aids and training materials, and

The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review, and regulatory authority inspections.

[redacted] Archiving

All study data must be archived for the longer of 3 years after study termination or premature termination of the clinical trial or as required by current local law. No source documents or study records will be destroyed without Sponsor notification and approval.

12. MONITORING PLAN

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the research requirements are met. Monitoring visits will oversee the progress of a clinical investigation and ensure that it is conducted, recorded, and reported in accordance with the protocol, written procedures, Good Clinical Practice (GCP) ISO 14155:2011, and the applicable regulatory requirements.

[redacted] Confidentiality and Data Protection

The investigator affirms and upholds the principle of the participant's right to privacy, and the investigator shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals.

Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor, a competent authority (CA), or an ethics committee (EC) may require direct access to parts of the medical records relevant to the study, including subject medical history.

[redacted] Storage of Images and Associated Health Data

PET/MR images and associated data will be collected and disclosed to the Sponsor as part of this study. Fully de-identified data, which has had all personal identifying information removed, may be stored and used by the Sponsor indefinitely. The Sponsor and/or its authorized representatives may use any de-identified data collected in this study for future technology and engineering development, marketing purposes, education, regulatory submissions, publications, or other possible uses.

[redacted] Publication Policy

The results of this study may be used in future publications as agreed between the Sponsor and site conducting the study. The conditions of publication are described in a separate contractual agreement.

REFERENCES

1. ISO. *Clinical investigation of medical devices for human subjects - Good Clinical Practice*: International Organization for Standardization; 2011. ISO 14155:2011(E).

2. Chen J, Zhao Y, Li X, et al. Imaging primary prostate cancer with 11C-Choline PET/CT: relation to tumour stage, Gleason score and biomarkers of biologic aggressiveness. *Radiol Oncol*. 2012;46(3):179-88.

3. Ortuño F, Lopez P, Ojeda N, Cervera S. Dysfunctional supplementary motor area implication during attention and time estimation tasks in schizophrenia: a PET-O15 water study. 2005;24(2):575-9.

4. Armbruster M, Sourbron S, Haug A, Zech C. Evaluation of neuroendocrine liver metastases: a comparison of dynamic contrast-enhanced magnetic resonance imaging and positron emission tomography/computed tomography. *Invest Radiol*. 2014;49(1).

5. Kamson D, Mittal S, Buth A, et al. Differentiation of glioblastomas from metastatic brain tumors by tryptophan uptake and kinetic analysis: a positron emission tomographic study with magnetic resonance imaging comparison. *Mol Imaging*. 2013;12(5):327–337.

6. Kitajima K, Suenaga Y, Ueno Y, et al. Value of fusion of PET and MRI in the detection of intra-pelvic recurrence of gynecological tumor: comparison with 18F-FDG contrast-enhanced PET/CT and pelvic MRI. *Ann Nucl Med*. 2014;28(1):25-32.

7. G D, Wiesinger F, Sacolick L, et al. Clinical evaluation of zero-echo-time MR imaging for the segmentation of the skull. *J Nucl Med*. 2015;3(417-22):56.

8. Sun Y, Ventura M, Oosterwijk E, Jansen J, Walboomers F, Heerschap A. Zero Echo Time Magnetic Resonance Imaging of Contrast-Agent-Enhanced Calcium Phosphate Bone Defect Fillers. *Tissue Eng Part C Methods*. 2013;19(4):281–287.

9. Center for Devices and Radiological Health (CDRH). Silver Spring, MD: US FDA; 2014. K142098.

10. Fornell. PET/MRI Enters the U.S. Market. *Imaging Tech News*. June 2011:1-4.

11. Brix G, Nekolla E, Nosske D, Griebel J. Risks and safety aspects related to PET/MR examinations. *Eur J Nucl Med Mol Imaging*. 2009;36(S1):S131-8.

APPENDIX A - STUDY SITE AND INVESTIGATOR LIST

The following investigator at the indicated site will be responsible for the conduct of this study:

Investigator: [1]	**Principal Investigator** Bradley J. Kemp, Ph.D. *Tel*: 1- 507-255-3614 *e-mail*: Kemp.Brad@mayo.edu	Mayo Clinic *Address*: 200 1st St SW Rochester, MN 55905

[1] The role of the ***Principal Investigator*** is to implement and manage the conduct of the investigation as well as ensure data integrity and the rights, safety, and well-being of humans involved in the study [ISO 14155:2011 9.1], as described in this protocol.

APPENDIX B - AMENDMENT TO PROTOCOL VERSION 1.0 TO 2.0

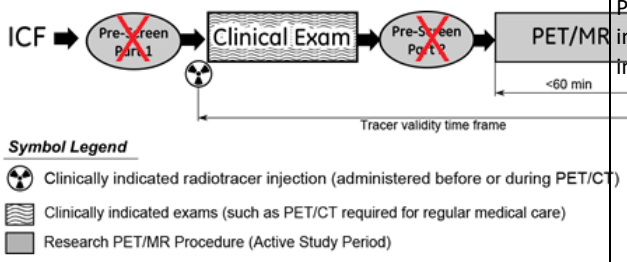
Purpose: This amendment document describes the changes from protocol version 1.0 to 2.0 to account for allowing patient with a pre-existing indication for PET/CT or PET/MR to participate. This does not change the safety profile or scientific intent of the study

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.

Item	Section	Revision or Clarification	Justification
1	Study Synopsis: Procedures/ Methods:	Adult subjects with pre-existing clinical indications for PET/CT or PET/MR with radiotracer injection will be enrolled to undergo up to 1 hour of PET/MR scanning within the tracer validity time frame in addition to~~after~~ their clinically indicated ~~PET/CT or PET/MR~~ exam. As part of the study, the corresponding PET/CT images will also be collected for ZTE subjects. Images collected from the sites will be post-processed outside of the clinical care environment by the Sponsor or its delegate using investigational MR post-processing software, and resultant images will be read by the site for diagnostic acceptability and by independent readers for scaled diagnostic image quality, as described in the Blinded Reader Evaluation (BIE) plan. The cumulative results of this study and concurrent studies of the device conducted by the Sponsor may be used to support regulatory submission of the devices under study.	To clarify that subjects with indications for PET/MR or PET/CT may participate (only PET/CT for ZTE testing).
2	Study Synopsis: Eligibility criteria:	2. Have preexisting clinical indication for PET/CT or PET/MR with radiotracer injection (for subjects that will undergo ZTE procedures, a preexisting clinical indication for PET/CT is required);	To clarify that subjects with indications for PET/MR or PET/CT may participate (only PET/CT for ZTE testing).
3	Section 2.1.1 Zero echo time (ZTE) Software Feature	The GE SIGNA PET/MR MP26 software platform includes the zero echo time (ZTE) scan for head attenuation and Q.Static. The ZTE MR software feature has the potential to enable better visualization of bones, including those in the head, by employing optimal head attenuation correction in PET/MR. ZTE functions serves a similar clinical purpose as ~~exist ant~~ existent visualization techniques (for example Atlas scans).	Typographical correction.
4	Section 2.1.2 Q Static (Q. MRAC) Software Feature	In addition, the platform will introduce an improved Q.Static feature with Q. MRAC, where phase matching the MRAC with the quiescent phase is employed ~~-~~to get more accurate attenuation correction for our Q.Static PET images. The planned new release of GE SIGNA PET/MR MP26 software platform introduces an improved Q.Static feature with Q.MRAC, which provides the ability to correct for respiratory motion during the MRAC portion of a PET/MR exam. It has the goal to create a quiescent (end expiratory) phase PET image with a phase-matched MR based attenuation correction, which is intended to provide more accurate attenuation correction for GE Q.Static PET images.	Added additional detail, as suggested by the site.
5	Section 2.3.1 Medications and Biologic Products	No medications or biologic products will be administered as part of the study procedures. Prior to participation in the study, subjects with clinical indications for PET/CT or PET/MR exams	Clarifies that patients with indications for PET/MR or PET/CT may participate, as

		will receive their clinically indicated injected radiotracer and any other medically necessary medications as ordered by their regular physician. Due to the in vivo half-life of radiotracer agents, it is reasonably expected that subjects participating in the study may have active radiotracer in their bodies during their PET/MR scan, but no additional radiotracers will be administered as part of the study. No sedatives or contrast agents will be administered for research purposes.	described in Amendments #1 and #2.
6	Section 2.3.2 Dosimetry	2.3.2 Dosimetry It is important to note that the patient will not receive a second radiotracer injection for the research PET/MR study. The residual radioactivity from the initial radiotracer injection of the clinical PET exam will be adequate.	Added section to clarify that no additional or increased dosages will be given of radiotracer or sedatives for research purposes.
7	Section 4.1 Study Population	Subjects will be enrolled that have a clinical indication for PET/CT or PET/MR with radiotracer injection prescribed for their medical care outside of the study. Sites should make reasonable attempts to ensure diversity of clinical state (including injury severity or extent of disease progression) within the enrolled population in order to achieve a sample maximally representative of the intended use population.	Clarifies that patients with indications for PET/MR or PET/CT may participate, as described in Amendments #1 and #2.
8	Section 4.2.1 Enrollment Quota	Subjects will be enrolled based on a quota block method based on scan type (relative to the patient clinical indication for PET/CT or PET/MR):	Clarifies that patients with indications for PET/MR or PET/CT may participate, as described in Amendments #1 and #2.
9	Section 4.4.1 Inclusion Criteria	2. Have preexisting clinical indication for PET/CT or PET/MR with radiotracer injection (for subjects that will undergo ZTE procedures, a preexisting clinical indication for PET/CT is required);	To clarify that subjects with indications for PET/MR or PET/CT may participate (only PET/CT for ZTE testing).
10	Section 4.5 Recruiting and Screening	Subjects will be recruited for potential enrollment in this study prior to their clinically indicated PET/CT or PET/MR exam according to the institutional procedures of the investigational site and its governing IRB. Participants identified after completing ~~the~~ their clinically indicated imaging ~~PET/CT~~ exam may be recruited, if otherwise eligible and within the study time window. All participation will be voluntary, and written informed consent will be collected from each participant prior to exposure to any investigational devices or procedures. Subjects will be screened for enrollment in this study against the inclusion and exclusion criteria according to the standard procedures of the investigational site. Following recruitment, a subject will be considered enrolled (the point of enrollment) once he/she signs and dates the informed consent form (ICF). Safety events and device issues will, however, only be reported during the period of exposure to the investigational PET/MR device (from the time the subject enters until the time the subject leaves the PET/MR suite), and not for clinically indicated imaging (e.g. PET/MR or PET/CT) ~~PET/CT~~ procedures that may be observed after the patient provides consent but are not a consequence of study participation. Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject. The unique subject number will be used to label	Clarifies that patients with indications for PET/MR or PET/CT may participate, as described in Amendments #1 and #2.

		case report form (CRF) data for the subject throughout his/her participation in the study.	
11	Section 5.1 Activities Prior to PET/MR (Pre-Screen)	**5.1 Activities Prior to PET/MR** For all subjects, s~~S~~tudy staff will confirm that the subject is eligible and complies with applicable site requirements prior to starting study procedures. After the subject completes the ICF, he/she will be required to complete certain ~~a two-part pre-screening procedure~~activities to participate in the study. ~~When possible, Part 1 should be completed before the subjects PET/CT exam.~~ **5.1.1 Pre-Screening Activities (All Subjects) ~~Part 1 (Before PET/CT)~~** • **Verify site institutional policy(ies) for MR safety are followed**. • **Record implant information** for subjects with implants allowable per the inclusion/exclusion that will be present during scanning (with the exception of passive dental filling/implants, surgical clips, or surgical staples)*, as follows: iv. Name of the device v. Manufacturer of the device vi. Model Number of the device ***Note**: If any or all information is not available, write N/A in the applicable area(s)* • **Record subject characteristics**, as follows: v. age (in years) vi. gender vii. weight viii. height **5.1.2 Pre-Screen ~~Part 2 (~~Activities ~~After~~for PET/CT Subjects~~)~~** • **Record clinically indicated PET/CT information** (before the PET/CT scan when possible to limit delay time between PET/CT and PET/MR), including start and end time of the PET/CT scan and information about injected radiotracer, as follows: iv. radiotracer type, dose and units, and time of injection v. clinical indication for PET/CT scanning (oncology, neurology, and/or cardiac etc.) vi. date and time of PET/CT • **Check for completeness** of acquired PET/CT images, if a subject is missing required PET/CT images, the subject may be withdrawn from the study. PET/CT images will be collected as part of the study. • **Check for solid food or insulin administration**. If a study subject is administered insulin, solid food, or any non-water beverage prior to the PET/MR imaging that can be expected to interfere with radiotracer activity, the subject may be withdrawn from the study at the discretion of the investigator if such administration(s) could interference with performing study procedures and/or radiotracer bioavailability during the study period.	Clarifies which screening elements are required for all patients and those only required for patients undergoing PET/CT or PET/MR.

		5.1.3 ~~Part 2 (~~Activities Required before Study PET/MR~~After~~ for All Subjects~~)~~ • **Encourage subjects to empty their bladder** prior to PET/MR scanning. • **Provide MR-safe clothing** according to participating investigational site's standard procedures, such as hospitals gowns, and isolate all non-MR compatible equipment or devices and route the devices and/or cables as required out of the magnet room. • **Provide mandatory hearing protection**, as per site institutional procedure.	
12	Section 5.2.1 Subject Procedure	Figure 1. Study procedure for PET/MR scans relative to clinically indicated imaging (PET/CT or PET/MR) with injected radiotracer  *MR Safety Screening and Pre-screening activities identified in Section 5.1 Activities Prior to PET/MR (Pre-Screen) should be completed prior to the start of the study PET/MR scan. The research PET/MR scan session will be performed while the subject is lying on a scan table. During this time, the subject may be asked to shift position to one side or another, lie still and to follow simple instructions such as to hold his/her breath at specified times. Subjects may be provided with a calling system that allows him or her to contact the Device Operator at any time during the scan. While the subject is in the scanner, the device operator will remain where the subject is visible (e.g. through a window) and audible (e.g. through an intercom). Start and end time of research PET/MR scanning and additional information will be recorded as per Table 2.	Modified Figure and Caption to reflect that PET/MR or PET/CT indications may be included.
13	Appendix A	Appendix B A – Study Site and Investigator List The following investigator at the indicated site will be responsible for the conduct of this study: **Investigator: [1]** | **Principal Investigator** Bradley J. Kemp, Ph.D. ~~Robert Witte, MD~~ *Tel*: 1- 507-255-3614 ~~507-284-2511~~ *e-mail*: Kemp.Brad@mayo.edu ~~witte.robert@mayo.edu~~ | Mayo Clinic *Address*: 200 1st St SW Rochester, MN 55905	Corrected typographical error in Appendix header. Added contact information for Co-investigator.


GE Healthcare

APPENDIX C - AMENDMENT TO PROTOCOL VERSION 2.0 TO 3.0

Purpose: This amendment document describes the changes from protocol version 2.0 to 3.0 to clarify that subjects will only receive one type of research exam (ZTE or Q.Static), not both.

The following amendments were made. 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
14	Study Synopsis: Procedures/ Methods	Adult subjects with pre-existing clinical indications for PET/CT or PET/MR with radiotracer injection will be enrolled to undergo a PET/MR exam lasting up to 1 hour ~~of PET/MR scanning~~ (which includes screening and approximately 30 minutes of scanning) within the tracer validity time frame in addition to their clinically indicated exam. During each scan, the operator will complete with the ZTE MRAC or Q Static (Q. MRAC) research protocol(s) appropriate for the subject's indication. As part of the study, the corresponding PET/CT images will also be collected for ZTE subjects.	Clarified that scan time is inclusive of screening and scanning.
15	Study Synopsis: Study duration	The study is expected to last about 2 months. Estimated start date: 01/~~Aug~~Oct/2016 Estimated end date: 01/~~Oct~~Dec/2016	Revises anticipated start/end dates to reflect current timelines.
16	Section 1. Background and Justification	This study is being conducted to demonstrate diagnostic image quality using the ZTE and Q.Static MRAC features in a representative sample of clinical cases requiring head and/or whole-body PET/MR scans.	Corrected terminology for consistency with other protocol sections.
17	Section 2.3.1 Medications and Biologic Products	No medications or biologic products will be administered as part of the study procedures. Prior to participation in the study, subjects with clinical indications for PET/CT or PET/MR exams will receive their clinically indicated injected radiotracer and any other medically necessary medications as ordered by their regular physician. Due to the in vivo half-life of radiotracer agents, it is reasonably expected that subjects participating in the study ~~may~~ will have active radiotracer in their bodies during their additional research PET/MR scan; therefore~~,~~ ~~but~~ no additional radiotracers will be administered as part of the study. No sedatives or contrast agents will be administered for research purposes.	Clarified language for transparency regarding anticipated incidental contrast agent administration. There is no intended change to study design or risk profiles based on these changes.
18	Section 3.3 Summary of Study Design	This is a pre-market, open label, prospective, non-randomized clinical research study at one site. The study is designed to allow for sample PET/MR image collection and to demonstrate diagnostic image quality of resultant sample image sets from each participating subject. The results of this study will be ~~read~~ analyzed according to a prospective Blinded Image Evaluation (BIE) plan and Statistical Analysis Plan (SAP) prepared by the Sponsor prior to the start of image reads. This study is run concurrently with other studies of the device conducted by the Sponsor and it is prospectively expected that the cumulative results of these studies may be used to support regulatory submissions.	Corrected typographical error.

<table>
<tr>
<td>19</td>
<td>Section 4.2.1 Enrollment Quota: Table 1</td>
<td>4.2 Number of Subjects
The study aims to acquire up to 75 clinical PET/MR image sets (up to 38 <s>using</s> subjects will be enrolled to have a<s>the</s> ZTE MRAC exam and the remaining 37 subjects will be enrolled to have a<s>using the</s> Q Static (Q. MRAC) <s>features</s>exam. In the event that a subject scan does not produce images, as in the case of withdrawal or technical issues preventing scanning, additional subjects may be enrolled until the target number is achieved (not to exceed a maximum of 75 subjects during the course of the study) as described in Section 10.2 - Sample Size Determination. The minimum number of necessary subjects will be enrolled to achieve the target number of datasets.
4.2.1 Enrollment Quota
Subjects will be enrolled based on a quota block method based on scan type (relative to the patient clinical indication for PET/CT or PET/MR). Each subject may have only one type of scan towards these quota blocks (ZTE or Q.Static MRAC), not both (Table 1).<s>:</s>
Table 1. Target quota blocks for subject enrollment/target datasets
<table>
<tr><th>Scan Type</th><th>Target number of subject datasets
(N_{Target} = 30)</th></tr>
<tr><td>ZTE MRAC</td><td>At least 30 subject scans
(N_{neuro} = 30 to 38)</td></tr>
<tr><td>Q Static
(Q. MRAC)</td><td>At least 30 subject scans
(N_{body} = 30 to 37)</td></tr>
</table>
</td>
<td>Clarified that subjects will only receive one type of research exam (ZTE or Q.Static), not both, and thus may fill only one quota block per subject.

Corrected terminology for consistency.</td>
</tr>
<tr>
<td>20</td>
<td>Section 5.1 Activities Prior to Research PET/MR Exam</td>
<td>5.1 Activities Prior to Research PET/MR Exam</td>
<td>Clarified that these procedures refer to the Research PET/MR exam.</td>
</tr>
<tr>
<td>21</td>
<td>Section 5.1.2 Pre-Screen Activities for PET/CT Subjects</td>
<td>• Record clinically indicated PET/CT information (before the PET/CT scan when possible to limit delay time between PET/CT and research PET/MR exam), including start and end time of the PET/CT scan and information about injected radiotracer, as follows:</td>
<td>Clarified that these procedures refer to the Research PET/MR exam.</td>
</tr>
<tr>
<td>22</td>
<td>Section 5.2 Activities during Research PET/MR Scanning and Data Acquisition</td>
<td>5.2 Activities during Research PET/MR Scanning and Data Acquisition
5.2.1 Subject Procedure
The site should perform research PET/MR scans during the time that the radiotracer validity time frame. Typically research PET/MR exams should be started with approximately 4 hours of radiotracer administration; however, the site may scan a subject at their discretion is the scan is expected to take place during the clinical validity window based on the investigator’s expertise (not required to be within 4 hours, Fig. 1). This is to ensure sufficient radiotracer activity during the investigational procedure.
…</td>
<td>Clarified that these procedures refer to the Research PET/MR exam.</td>
</tr>
</table>

		The PET/MR exam may last up to a 1 hour (which includes screening and approximately 30 minutes of scanning). Start and end time of research PET/MR scanning and additional information will be recorded as per Table 2.	
23	Section 5.2.2 ZTE MRAC and Q Static (Q. MRAC) PET/MR Scanning Procedure	During each scan, the operator should complete ZTE MRAC ~~and/~~or Q Static (Q. MRAC) protocol~~(s)~~ appropriate for the subject's indication ~~(both when clinically possible)~~, and record the sequence used in the exam. For Q Static (Q. MRAC) scans, the site should conduct 5 non-gated MRAC acquisitions and 5 gated acquisitions for each subject around the lung/abdominal region including the diaphragm.	Clarifies that subjects will only receive one type of research exam (ZTE or Q.Static) not both.
24	Section 5.2.4 Incidental Findings	The additional PET/MR procedures performed in this study are for research only and are not intended for diagnostic use. Should the device operator observe what they interpret to be a potential abnormality, the investigator will evaluate the findings and alert the patient if necessary. The investigator may recommend diagnostic exams to be performed independent of the study. No medical or diagnostic care of any kind will be rendered based on study image sets using the research PET/MR.	Clarified that these procedures refer to the Research PET/MR exam.

APPENDIX D - AMENDMENT TO PROTOCOL VERSION 3.0 TO 4.0

Purpose: This amendment document describes the changes to a remove legacy element in Table2 that inadvertently was included in this version when amendment 3.0 was approved in the Sponsor's MWS documentation system.

The following amendments were made. Point-by-point revisions are shown as additions in double-underline (<u>double-underline</u>) 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>25</td><td>Section 5.2.2 ZTE MRAC and Q Static (Q. MRAC) PET/MR Scanning Procedure: Table 2</td><td>
<table>
<tr><th>Coil(s) Used</th><th>Gating device(s) used</th><th>Medical tubes wires/cables</th><th><s>Subject Motility</s></th></tr>
<tr><td>• 3.0T PET/MR CMA
• 3.0T HNU
• 3.0T UAA
• 3.0T LAA
• GEM Flex Coil 16-S, M, L Array
• 3.0T Split head coil
• PETMR 8Ch HiRes Brain Array
• 3.0T HD Flat GEM Table Breast Array
• Other, specify</td><td>• Respiratory bellows
• ECG leads
• Peripheral gating photopulse sensor</td><td>• None
• IV
• Catheterization
• Breathing tube
• Oxygen
• ECG Monitor
• Other, specify</td><td><s>• Walk in on own
• Needs wheel chair
• Lifted onto table
Needs assistance walking in</s></td></tr>
</table>
</td><td>Remove legacy element in Table 2 that inadvertently was included in this version when amendment 3.0 was approved in the Sponsor's MWS documentation system.</td></tr>
</table>

End of Document