GE Healthcare

Study Title: Development of a MR Scanner Capable of Being Sited in a Neonatal Intensive Care Unit
Study Number: 114-2014-GES-0035
Revision/Amendment: 7.0
Version Date: 25/Sep/2015

Confidentiality Statement

Development of a MR Scanner Capable of Being Sited in a Neonatal Intensive Care Unit
GEHC Study Number: 114-2014-GES-0035
Revision/Amendment: 7.0
Version Date: 25/Sep/2015

Investigator's Signature Page

I hereby agree to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, applicable MHRA 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 _____

Table of Contents

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	28/Oct/2014	Angela Johnson	Clinical Writer- Initial draft.
2.0	03/Dec/2014	Angela Johnson	Updated name of medical monitor, as detailed in Appendix H: Amendment to Protocol Version 1.0
3.0	04/Mar/2015	Angela Johnson	Revised to clarify that the primary endpoint of the study is in accordance with Section 2.1 of Annex X of the EU Medical Devices Directive, which species that verificatio of performance and safety across the study cohort is an essential requirement of the study; details local site feed and sleep procedures; and clarifies the duration of the study at planned for 24 months, as detailed in Appendix I: Amendment to Protocol Version 2.0
4.0	26/Apr/2015	Angela Johnson	Revised to clarify per MHRA questions, as detailed in Appendix J: Amendment to Protocol Version 3.0
5.0	15/May/2015	Angela Johnson	Revised to clarify per MHRA questions, as detailed in Appendix K: Amendment to Protocol Version 4.0
6.0	13/Aug/2015	Angela Johnson Yvonne Celestial Lisa Augustine	Revised to clarify modifications made in prior version, as detailed in Appendix L: Amendment to Protocol Version 5.0.
7.0	25/Sep/2015	Angela Johnson	Revised to clarify modifications made in prior version, a detailed in Appendix L: Amendment to Protocol Version 6.0.

ABBREVIATIONS AND TERMS

CHF	Clinical History File
CRF	Case Report Form
DMP	Data Management Plan
EU	European Union
FDA	US Food and Drug Administration
ICF	Informed Consent Form
ISO	International Organization for Standardization
MHRA	Medicines and Healthcare Products Regulatory Agency
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NICU	Neonatal Intensive Care Unit
PDU	Power distribution unit
PNS	Peripheral nerve stimulation
RF	Radiofrequency
SAR	Specific Absorption Rate
SNR	Signal to noise ratio
SPR	System problem report
SUS	System Usability Scale
TiP	Training in Partnership
TVA	Tip Virtual Assist (Remote Connectivity)
UK	Unites Kingdom
US	United States
UXS	User Experience Scale

STUDY SYNOPSIS

Study Title: Development of a MR Scanner Capable of Being Sited in a Neonatal Intensive Care Unit
Study Number: 114-2014-GES-0035

Research Type

Clinical (human)	☒ *Viable neonate and infant populations*
Pre-Clinical (animal)	☐
External Bench	☐

Brief Description of Study Purpose

This study investigates a novel magnetic resonance imaging (MRI) system designed by GEHC for imaging viable neonate and infant populations. This MR system has a smaller size and design features that may make it more feasible to locate the system in close proximity to care areas for neonates (birth – 1 month) and infants (>1 month to two years), such as clinical neonatal intensive care units (NICUs) and other infant and neonatal care departments

This is a two-phase prospective clinical study evaluating the performance and safety of the investigational MRI device for neonates and infants, including:

- Phase 1 - Initial feasibility assessment and optimization study (Phase 1) which may include hardware and software modifications. These studies are guided by a series of MR scanning procedures defined in sequential Sponsor-provided *MR Procedure Documents*
- Phase 2 - Controlled image and data collection study based on Phase 1 results, in which optimized scan procedure(s) according to *MR Procedure Document(s)* will be provided at the start of Phase 2 scanning and a fixed hardware and integrated software configuration will be applied for all subjects.

Investigator feedback on scanning conducted under each *MR Procedure Document* will be documented. Because the device is intended for use in viable neonate and infant populations, clinical data are required that cannot be conducted in any other populations or simulated on non-human models. Clinical images and associated data as well as assessments of image quality, workflow, and usability will be collected.

Images, associated image data, and subject data collected in both phases of this study may be used for future engineering development and activities that support MR product development, including Sponsor-authorized scientific and marketing activities. Summary evaluation of safety and performance from Phase 1 and Phase 2 may be used in support of regulatory submission, including filings for European CE mark.

Sponsor Name: GE Healthcare (GEHC) *Sponsor contact*: Yvonne Celestial, Clinical Affairs Project Manager	**Address**: 283 rue de la Miniere Buc, 78533, FR **Telephone**: +33 130709133 **E-mail**: MarieYvonne.Celestial@ge.com
Investigator Name(s) Prof. Paul Griffiths, MB, ChB, PhD Academic Unit of Radiology University of Sheffield Floor C, Royal Hallamshire Hospital	**Address**: Glossop Road Sheffield, UK S10 2JF **Telephone**: +44 (0) 114 271 2587 **E-mail**: p.griffiths@sheffield.ac.uk
Device/Product GEHC Modality: MR	

Device/Product Description: Small-footprint 3.0T Neonatal MRI investigational device capable of being located in a NICU and its components, including a single-use disposable swaddle, sizing ring, and transport devices. The device design is based on commercially available Optima MR430s 1.5T, Discovery MR750 3.0T, and SIGNA HDx MR technologies and commercial Sponsor-provided patient monitor (Invivo Corp) and site-owned protective devices (e.g. hearing protection and, if necessary, padding or blankets) will be used.	
Regulatory Status: Pre-Market ☒ 3.0T Neonatal MRI investigational device, its components, and its accessories (Single-use disposable swaddle, Sizing ring, and Transport devices) Post-Market ☐	
Duration: The study plans to enrol patients for approximately 24 months.	
Research Manager Name Lisa Augustine Warren, Research Project Manager, Global MR Research	**Address**: 3200 N Grandview Blvd Waukesha, WI 53188-1678 **Telephone**: +1-440-250-9488 **E-mail**: Lisa.Augustine@med.ge.com
Medical Monitor Name: Jeff Hersh, MD	**Address**: 3200 N Grandview Blvd Waukesha, WI 53188-1678 **Telephone**: +1-262-366-7295 **E-mail**: Jeff.Hersh@ge.com

1.1. Preliminary Investigations and Justification

1.2. Literature Review

Demand for postnatal magnetic resonance imaging (MRI) examinations in clinical settings is growing rapidly, in part due to recent improvements in neonatal survival rates and antenatal diagnostic imaging. The US Food and Drug Administration (FDA) defines infants (>1 month to 2 years) and neonates (birth to 1 month) by approximate age and weight. [1] In particular, neonatal MRI has become standard clinical care for neurological and orthopaedic applications at many clinical facilities. [2,3,4,5] Despite this increasing application of MRI to very young subjects, MRI has not been specifically optimized for imaging infants and neonates outside of a few limited research settings. [6] The challenges of neonatal MRI imaging have been extensively documented, [5,4,6,7] leaving significant room for improvement in MRI scanning of neonates to make MRI more practical and comfortable for these vulnerable subjects and their care providers.

MRI is useful for examining neurological disease in the developing brain of young subjects, and MRI also serves a key diagnostic role for a variety of other conditions and abnormalities in developing neonate and infant anatomy. The clinical manifestations of neurological disease are more subtle during early neurological scanning in infants and neonates, and many neural structures that are central to the adult human brain cognitive function are functionally silent in the infant. [8] This poses unique challenges for applying MRI effectively in this population. MRI systems have also been used for orthopaedic, thoracic, and abdominal exams in the first hours of life with good results, though there remains significant room for improvement and optimization of these systems for neonates and infants. [9] In a variety of anatomical regions, high-quality images have been attained with good spatial resolution, signal-to-noise ratio, and tissue contrast using standard clinical MRI protocols in infant and neonate subjects housed in the NICU environment, but the logistics of transport and safety for these subjects remains challenging in most clinical facilities. [9]

In preterm neonates, there is an even more pronounced disconnect between adult and neonatal MR image characteristics, resulting in significant risks associated with misinterpreting MR images resulting from using scanning techniques optimized for adult or older paediatric subjects. [8] Advances in antenatal diagnosis of brain, spine, and body abnormalities as well as diagnostic imaging for specialized conditions, such as ischemic encephalopathy, that rely on MR imaging systems have increased demand for postnatal MRI. [10,8,11] Thus, there is a growing need for high-resolution MR images of the neonatal and infant brain, along with numerous possible clinical and research applications of such imaging.

For neonatal MRI, the vast majority of clinical care facilities use a conventional commercial whole-body MRI system with standard, commercially available coils, though custom-built systems and systems that integrate commercially available incubators have been documented. [12,13,14] Because of the advantage of neonatal MRI, a growing number of clinical facilities are considering installing dedicated neonatal imaging systems that are optimized both logistically, in terms of location relative to the NICU and other infant/neonatal care departments, and in terms of subject care. [15] Recently, a small profile 1.5T MR system has been built by Cincinnati Children's Hospital Medical Center for neonatal MRI and is sited in the neonatal intensive care unit at that institution. [13]

In contemporary clinical practice, there is a growing unmet need for MRI imaging systems that are specifically designed for use in neonatal and infant populations. Though off-label use

of MRI systems approved for adults does occurs in some clinical settings, MRI is still not accessible to the majority of neonates and infants in the current paradigm, and the current trend is away from off-label use of adult devices on infants and neonates. [2] Furthermore, the hardware and software developed for adults is being applied to neonates, often in a suboptimal manner that could involve yet unknown risks and reduce performance in this vulnerable population. [2] There are also notable risks involved in transporting infants from a neonatal intensive care unit (NICU) to a radiology department for MRI, both logistically and medically. [16]

The development and regulatory approval of dedicated MRI systems for neonates and infants may make MRI more widely available to these populations in clinical care settings. The potential advantages of dedicated neonatal MRI systems may include overall reduced cost and site demands, lower acoustic noise, improved ease of access, and reduced medical risk to the neonate. [16] This study investigates a dedicated MRI system developed by the Sponsor for imaging viable neonate and infant subjects.

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

Research and clinical use of MR imaging has been widely documented in scientific literature over the past three decades, including research as early as the 1980s. [17,18,19,20] Recommendations have also been made by the American Academy of Neurology and Child Neurology Society [10] to help guide clinical practice when imaging preterm and term infants, stating that "MRI holds great promise; however, this imaging modality and others that may be soon developed must become more infant friendly, and imaging strategies should be developed to provide maximum information in minimum time." Extensive scientific literature exists to support the safety and effectiveness of MRI executed by properly trained operators for neonate and infant populations; [21,22,23,24] however, the physiologic differences in the neonate and infant brain compared to adults leaves room for optimization of MR hardware and software to produce improved results in these populations. [25]

GEHC has not previously conducted clinical studies using the 3.0T Neonatal MRI investigational device under study. A second study using this device in the United States (US) is currently being planned.

1.4. Device Risk Analysis

1.4.1. Risks

The 3.0T Neonatal MRI investigational device is intended for use in neonates and infants, and its components and accessories used in this study are based on similar commercial systems labelled for use in patients aged greater than 2 years of age and manufactured by the Sponsor, and these devices have undergone non-clinical qualification and risk assessments conducted by the Sponsor. Participating in this study involves some risks that are unique to the design of the scanner and population (neonates and infants), as described Section 11.1 Foreseeable Adverse Events. This section lists possible foreseeable adverse events and device effects, but actual occurrences of these risks are uncommon and are not anticipated to occur frequently, if at all, in this study. While serious adverse events can occur in MRI exams in rare cases, typically with adverse events occurring as a result of failure to correctly follow routine site MR safety procedures for scanning, no serious adverse events are anticipated in this study.

Subjects participating in research MRI scanning in this study are not expected to be at increased discomfort or risk beyond that posed by other standard of care MRI devices. The investigational single-use disposable swaddle is a medical device that is expected to have risk comparable or less than routine MR padding, blanketing, and/or other transportation devices. During the study, the subject will be transported and cables or other devices may be disconnected or connected, which could cause discomfort or interruption of care. The investigator is responsible for ensuring minimal disruption of normal care during the study.

1.4.2. Benefits

Subjects are not expected to directly benefit from participating in this study, and no diagnostic or other care will be determined based on research MR scanning in this study.

2. RESEARCH DEVICE AND/OR PRODUCT

2.1. Identification and Description of Research Device/Product

2.1.1. 3.0T Neonatal MRI Investigational Device

The investigational device being studied is a 3.0T Neonatal MRI device intended for use in neonates and infants. The device has a small size profile that makes it capable of being sited in a NICU or other neonatal and infant care units. This device includes an MR system and its hardware and software components is a whole body magnetic resonance scanner designed to support high resolution, high signal-to-noise ratio and short scan times. It is indicated for use as a diagnostic imaging device to produce axial, sagittal, coronal, and oblique images and proton spectra of the body of neonates and infants. It is specifically designed so that the system is able to be sited in or near NICUs, including having smaller overall dimensions and weight compared to conventional commercial whole-body MRI scanners. This reduces the structural and space requirements for housing the device. Many components of the device are based on engineering designs used in the commercially released Optima MR430s 1.5T, the Discovery MR750 3.0T, and the SIGNA HDx Family of MR systems.

The device is also designed with accessories to make transport of the neonatal subject from the bedside to the MR scanner more efficient. Image data produced by the 3.0T Neonatal MRI investigational device is capable of reflecting the spatial distribution or molecular environment of nuclei exhibiting magnetic resonance. Due to the nature of this research study, the device will not be used diagnostically for the purpose of this study, and study scans are conducted for research purposes only.

2.1.2. 3.0T Neonatal MRI Investigational Device Components and Initial Configuration

The configuration of the device at the beginning of the study includes the central hardware and software components, as follows:

System Hardware Components

1. **3.0T Magnet**: The device uses a 3.0T magnet based on GEHC's commercially released Optima MR430s 1.5T musculoskeletal MR system. The device's 3.0T magnet, unlike predecessor 1.5T magnets, is designed to increase image signal-to-noise ratio which is important in imaging this subject population in order to maximize tissue contrast in the images.

2. **17.86 cm (diameter) Bore:** The bore is the opening in the center of the device in which the subject is placed during MR scanning. Color-coded landmarking controls are used to assist in positioning subject anatomy in the bore.
3. **Gradient Coils and Gradient Drivers (70 mT/m gradient strength and 300 T/m/s slew rate):** The gradient system used in the device is based on the combined technologies of the Optima MR430s 1.5T and SIGNA HDx series MR systems with adapted HDx gradient driver technology. Magnetic gradients are slight changes in the main magnetic field due to three electrically controlled orthogonal coils oriented in the x, y, and z directions of the scanner. These gradients are involved in signal localization and imaging plane selection (axial, sagittal, coronal, and oblique).
4. **Radiofrequency (RF) System:** The RF transmitter consists of an exciter (synthesizer), power amplifier, and transmitting/receiving coil. The exciter design is based on the commercially released Discovery MR750 3.0T system, and the amplifier is a new design specifically made for this device. The RF device consists of a coil, pre-amplifier, and signal processing system. The transmitting and receiving coil is a single channel sixteen rung "birdcage" coil (inner surface accessible to the subject). The RF transmits proton-exciting energy into tissues, and subsequent proton relaxation energy emission is detected by receiver RF coils. This data is processed into MR images. The closer fit to specific neonate anatomy is intended to improve RF signal detection in order to improve image quality.

   Transport Cart (Table): The small profile transport cart docks to the MR scanner table for bedside-to-MR transport within space-limited care areas for neonates and infants, such as NICU environments.

System Software Components

All of the pulse sequences, post-processing, and visualization software are based on, and are similar in design and function to other commercially released software for GEHC MR scanners. Software components that may be variably used in this study are detailed in Appendix D – Example of Possible Software Components. These include the following primary software components:

1. **Pulse Sequences:** Pulse sequences are software sets of RF (and/or gradient) magnetic field pulses and time spacing's between these pulses that can be used in conjunction with magnetic field gradients and MR signal reception to produce MR images. These software sets are installed on the system and are thereafter available for use with specific operator-set parameters. The pulse sequences being studied are similar in design and function to commercially available pulse sequences. The type of pulse sequence and parameter settings that dictate the timing and shape of the pulses provide the operator control over the image contrast. In most clinical MR exams, images are acquired with multiple pulse sequences with various settings, allowing clinicians to compare and distinguish tissues and abnormalities. The site may also provide phantoms for study use.
2. **MR Post-Processing and Visualization Software:** Post-processing and visualization software are software modules and/or algorithms that manipulate the images for purposes such as, but not limited to, changing the characteristics of the images and generating parametric maps and related reports.

Additionally, services and accessories that are intended to work with the device may be used in this study, as follows:

System Accessories

1. **Straps**: The straps secure the patient to the table during the scan.
2. **Sizing guide (sizing ring tool)**: The sizing ring tool is a horseshoe-shaped component used to ensure the patient (with all required accessories) will fit into the bore of the MR device.
3. **Neonate MR Padding**: Special padding for neonates and infants has been designed to work with the investigational device.
4. **System Service Tools/Phantoms (Simulations)**: Phantom images are simulations of human scanning that can be completed without a real human subject in the magnet bore. During the study, the Sponsor and the investigator may generate and run phantom imaging procedures on the device. Phantoms may be provided for training, education, engineering, and optimization purposes.
5. **Remote Connectivity**: The device is capable of remote connectivity through the Training in Partnership (TiP) Virtual Assist (TVA) program, which offers secure data connections between a Sponsor representative and the device user for use in training, trouble-shooting, and real-time image quality optimization during scanning.

2.1.3. Single-use Disposable Swaddle

The single-use disposable swaddle is an investigational medical device that is a soft, pliable, blanket-type accessory with Velcro® closures intended for swaddling infant or neonate subjects on both sides and feet before, during, and immediately after MR scanning. The swaddle has been designed for patient transfer and positioning and allows the infant to be securely positioned and immobilized during the lift and transfer process. The swaddle also provides line management for any gating wires and/or tubes that may be attached to the infant and to any devices. The swaddle is disposable and intended for single-use only. It is considered to be an accessory to the MRI system that contains the following key components:

1. **Velcro® closures**: Internal and external closures secure the infant/neonate using Velcro® straps.
2. **Textile material**: Swaddles are constructed of soft, dual-layer, pliable, blanket-type textile materials.
3. **Backboard**: The backboard is a non-disposable component that can be optionally used with the single-use disposable swaddle to stabilize larger subjects.

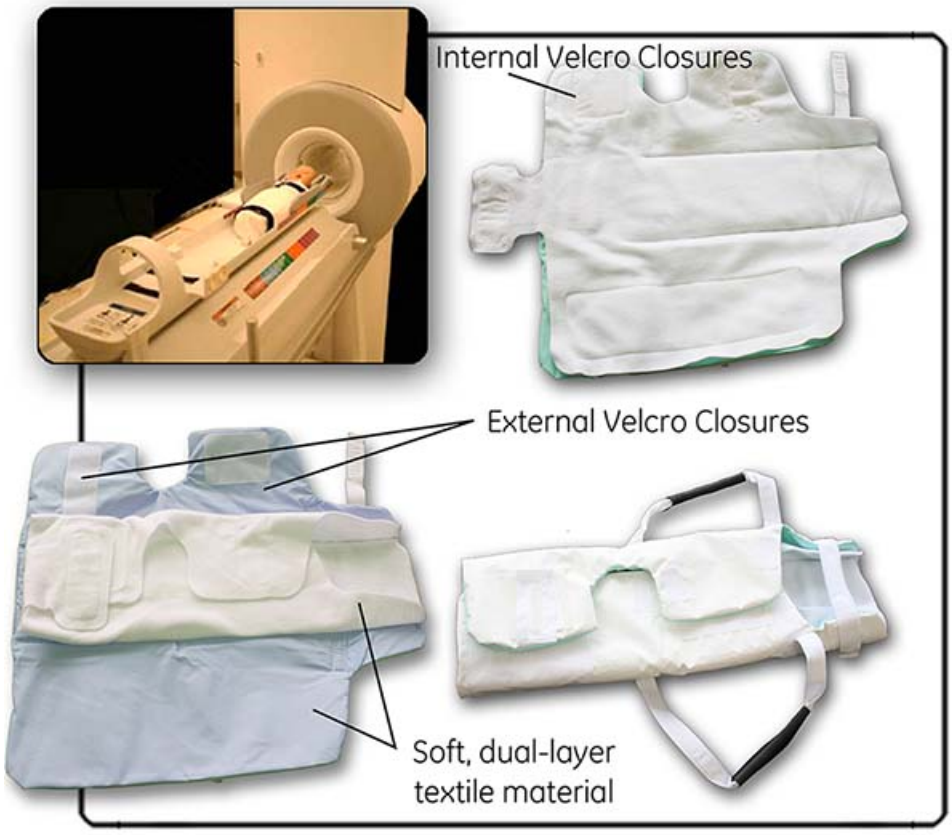


Figure 1 – Image of swaddled neonate entering the 3.0T Neonatal MRI investigational device bore (*top left*) and views of soft, dual-layer textile swaddle showing Velcro® closures.

2.1.4. Other MR Equipment

The Sponsor may also provide other commercial MR equipment required to conduct the study, including:

a. physiologic motion synchronization devices,
b. protective padding,
c. hand-held metal detector,
d. patient monitoring equipment (i.e. Invivo Corp monitor), and
e. other commercial MR accessories

There may be other commercial equipment provided to the investigational site(s) as part of this study. All commercial equipment provided to the investigational site will be documented in the Sponsor's Clinical History File (CHF) in the *Device Accountability Log* and communicated in writing to the investigational site. The intent to use any other commercial MR accessory devices that are not explicated described in the protocol procedures during clinical scanning procedures will be documented in the Sponsor-provided *MR Procedure Document* and records will be retained in the *Device Accountability Log*

Expression Patient Monitor (Invivo, Corp; Orlando, FL, USA)

Expression Monitor (Invivo Corp) – This is an MR Conditional patient monitor system labelled for use in neonate and infant populations that can remain in the magnet room during scanning. Depending on workflow, this can also be sited near the operator console for patient monitoring during the MR scan.

Invivo Corp patient monitor will be used during study procedures to monitor subject vital signs, body temperature (on the Expression Monitor using a single-use sensor in the MRI scan room), and O_2 saturation.

2.1.5. Device Configuration Management

Throughout Phase 1 (Feasibility and Optimization) part of this study, the configuration of the device, including hardware and software components, may be altered for engineering research and optimization purposes to gain *in vivo* human data about the optimal device configuration. For Phase 2, a single device configuration will be used.

The Sponsor will ensure that changes in device configuration will:

a. Not increase risk classification of the study;

b. Not increase subject and/or operator risk;

c. Be released internally by the Sponsor prior to release to the investigational site;

d. Be communicated in writing to the Principal Investigator (PI) and stored in the Sponsor's Clinical History File (CHF); AND

e. Be accompanied by appropriate training materials related to changes in device configuration, if determined to be necessary by the Sponsor or upon request of the PI.

Note: No changes in device configuration will be implemented that are not communicated in writing by the Sponsor to the Principal Investigator and stored in the Sponsor's Clinical History File (CHF) as part of the *Device Accountability Log* and maintained in the *Site Regulatory Binder*

For changes in device configuration, the Principal Investigator assumes responsibility for:

a. Providing confirmation of device configuration changes and ensuring that these are stored in the *Site Regulatory Binder*;

b. Ensuring that Sponsor-provided communications or electronic copies thereof are stored in the *Site Regulatory Binder*;

c. Ensuring that Study Staff are trained and documentation is retained of such training for Sponsor-provided training materials and, as necessary, changes to device configuration and records.

Note: The PI may request additional training from the Sponsor if necessary, at his or her discretion. All training will be documented. In addition to Sponsor-provided training, the PI and designated study staff may perform phantom scanning not using human subjects for the purpose of training and retraining staff members at any time during the study.

2.2. Regulatory Status

The 3.0T Neonatal MR investigational device is a pre-market magnetic resonance diagnostic device and its accessories and components are not yet cleared for commercial use (pre-

market). In the United Kingdom (UK), the use of the device is subject to regulation by the Medicines and Healthcare Products Regulatory Agency (MHRA), in compliance with the Medical Devices Regulations of 2002 (transposition of European Medical Device Directive 93/42/EEC concerning medical devices, including Articles 3, 15, Annexes VIII and X).

The Expression MRI patient monitoring system (Invivo, Corp; Orlando, FL, USA) provided by the Sponsor for use in this have received CE mark for commercial use and are labelled for use in neonate and infant populations. All patient monitoring equipment will be used in accordance with its labelled indications, including meeting all conditions for MR scanning for MR Conditional devices.

2.3. Risk Categoryand Rationale

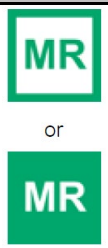
The MRI device used in this study uses static magnetic field strengths <4.0T, which are widely accepted to pose minimal risks to typical adults, children, and infants/neonates, as detailed in the US FDA Guidance *Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices* and contemporary medical literature[26, 27]. During this study, subjects will encounter routine risks of transport outside of their regular care environment, which are considered mitigated to levels as low as reasonably practicable (ALARP) by design of the device and attendance of medical personnel throughout the subject's transport and study procedures. The 3.0T Neonatal MRI investigational device under study uses a 3.0T static magnetic field. The Sponsor's Risk Management procedures demonstrate that risks have been appropriately mitigated according to ISO 14971, in compliance with regulatory requirements set forth by the Medicines and Healthcare Products Regulatory Agency (MHRA), in compliance with the European Medical Device Directive 93/42/EEC.

2.3.1. MR Safe, Conditional, and Unsafe

Some medical devices placed into surgically or naturally formed cavities of the human body (implants) or other device or objects outside of the body may be allowed into the MR environment; however, MRI examinations may be contraindicated in patients with some types of passive or active implants that cannot be safely allowed in the MR environment. If these procedures and the site MR safety policy are followed, the risks associated with devices and objects within the MRI environment are considered to be no greater than routine clinical MRI scanning.

ASTM F2503 *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment* provides terminology for classifying whether implants pose

potential hazards to patients in the MR environment that is recognized in the European Union and United States Food and Drug Administration (FDA),[1],[2] as follows:

Label	Description (typical use)
	MR Safe
	MR Conditional
	MR Unsafe

Note: If the level of MR compatibility of the device in question is not known (not presented on the device label) or the device identity is not able to be determined, then an implantable device should be considered MR Unsafe for the purposes of this study, with the exception of dental devices/fillings, surgical clips, and surgical staples determined to be safe for MRI scanning by a physician investigator.

Special care should be taken in MRI with metal objects typically found on neonates and infants, such as umbilical cord clips and identification bands. The local site MR safety policy should be followed when determining if these devices are safe for MRI.

2.4. Device Classification and Rationale

In the United Kingdom (UK), the investigational 3.0T Neonatal MRI investigational device and its components and accessories used in this study are considered a Class IIa medical device per the European Medical Device Directive Annex IX, Rule 10. The Single-use Disposable Swaddle and its components and accessories are considered to be a Class I medical device per the European Medical Device Directive Annex IX, Rule 10.

In the UK, the Expression MRI patient monitoring systems (Invivo, Corp; Orlando, FL, USA) are considered Class IIa medical device per the European Medical Device Directive Annex IX, Rule 10.

2.5. Device Issuance and Replacement

2.5.1. Issuance and Installation

The Sponsor will ship to the study site and install the investigational 3.0T Neonatal MRI investigational device. The Sponsor will provide single-use disposable swaddles and

[1] Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment. US Food and Drug Administration (FDA). August 21, 2008, updated April 6 2011.

[2] European Union (EU) Directive 2004/40/EC and 2008/46/EC

necessary hardware and software components and accessories for the investigational system.

If not already owned by the investigational site, the Sponsor may provide each site with Sponsor-owned Expression (Invivo Corp) patient monitoring systems labelled for use in neonate and infant populations according to MR Conditional labelling. Unique identifying information will be recorded for both Sponsor-provided and site-owned devices used in this study and a copy of this information will be stored in the Sponsor's *Device Accountability Log* stored in the Clinical History File (CHF).

2.5.2. Medicinal and Biologic Product Administration and Delay

No clinically indicated medical care will be additionally administered or delayed for any subject due to study participation. No medicinal agents (including sedatives), biologically active agents, or contrast agents not required for the subject's clinical care outside of this study will be administered for the purpose of this study, with the exception of routine sweet solutions ('sweeties') which may be used during the study period if prescribed by a physician.

Subjects that received sedatives or other clinically indicated medicinal or contrast agents as part of their regular clinical care may be included if there are no extensions of administration or delays to administration of clinically indicated medications (including treatments required to end sedation) as a result of study participation. Sedation may not be extended for the purpose of this study.

2.5.3. Future and Concurrent Use of Devices

This study is being conducted for engineering development and regulatory submission (including CE mark in the EU) of an investigational medical device and its components and accessories. After the device is CE marked, the device and/or its components may be used concurrently in other research activities in the EU under EC/IRB approved protocols, subject to, and required to adhere to, applicable local laws and regulations, and to the requirements of the Sponsor for device accountability. Any concurrent research activity will also be required to receive approval from the Sponsor and the institutional EC/IRB at the investigational site(s). This information may also be used for regulatory purposes in other countries outside of the EU. If the device is used in other countries, future and concurrent use will adhere to applicable laws and regulations.

2.5.4. Research Device Labelling

The device and related components will be labelled as an investigational device in accordance with local regulatory requirements in the UK. Labeling for investigational device(s) shall be provided by the Sponsor in a format approved by the Sponsor and consistent with local regulatory requirements at the investigational site.

2.5.5. Maintenance and Replacement

During this study, the Sponsor will be conducting engineering optimization and ensuring that the device(s) operate as intended, which may involve maintenance or replacement of hardware or software components of the device(s) and device accessories at the investigational site(s). To this end, Sponsor-authorized personnel may:

a. Access device(s) in-person or remotely (such as through TVA/TiP or other secure remote connection) for quality control, trouble-shooting, training, real-time image optimization, to collect system configuration and system log files, or other purposes required for device maintenance, installation, de-installation, and/or system data collection;
b. Conduct phantoms (simulated non-human) scans;
c. Repair or replace the device or any of its components;

The Principal Investigator (PI) assumes responsibility for promptly reporting any device-related adverse events or product complaints observed by the PI or study staff to the Sponsors Clinical Affairs Project Manager (CAPM).

2.5.6. Security for Investigational Devices

1. **Single-use DisposableSwaddles:** Single-use disposable swaddles and non-disposable backboards will be uniquely and sequentially numbered and stored in a locked cabinet accessible to study staff. The investigational site will log the use and disposal of each swaddle (Appendix B). Swaddles are intended for use with the investigational device under this protocol, and swaddles may not be used outside of a Sponsor- and EC/IRB-approved study protocol. Each swaddle may be used only once, and may only be used on a single subject.
2. **Power Distribution Unit** : The Sponsor may lock the Power Distribution Unit (PDU) to secure the investigational device if changes are made to the device configuration requiring additional study staff training or maintenance.
3. **Host Computer**: The host computer will accessible to authorized study staff, including the PI and trained scan operators, with a Sponsor-provided username and password.
4. **Security for the MR Environment** The investigational device will be housed in a secured environment that meets the Sponsor's engineering specifications for device installation. This area and the entrance to the scan room will accessible only to the PI and trained study staff. The Principal Investigator assumes responsibility for meeting all investigational site and Sponsor requirements for securing the device.

2.6. Disposition of the Device/Product

When scanning under EC/IRB approved study protocols, the following actions will be conducted:

a. The Sponsor will ensure that the device(s) and its components are dispositioned according to the contractual agreement reached between the investigational site and the Sponsor, in accordance with applicable local laws and regulations.

b. The Investigator will ensure that used disposable components, such as used swaddles, will be handled according to the investigational site(s) standard procedures for disposal of biomedical waste.

c. The Investigator will ensure that unused disposables and other non-disposable equipment provide by the Sponsor (including any Sponsor-provided Invivo Corp Expression patient monitor, hand-held metal detectors provided by the Sponsor, and the non-disposable backboard for the swaddles) are returned to the Sponsor.

3. OBJECTIVES OF RESEARCH STUDY

3.1. Hypothesis

There is no statistical hypothesis being tested in this study. Descriptive statistics will be used to provide summary evaluations of performance and safety data.

3.2. Justification

This study is being done in two parts to optimize and collect data from a new MRI device for use in neonates and infants, the 3.0T Neonatal MRI investigational device. The first part of this study is being conducted to demonstrate the feasibility and safety of attaining diagnostic quality images and data using the 3.0T Neonatal MRI investigational device in neonates and infants with various hardware and software configurations. The second part of this study is being conducted to collect images and associated data in neonates and infants from a fixed hardware and software configuration of the 3.0T Neonatal MRI investigational device in support of regulatory activities in the European Union (EU), including CE mark. MR system log files containing operating parameters relative to safety and performance calculations will be systematically collected throughout the study for all subjects. Summary performance and safety evaluations from both parts of the study may be disclosed to regulatory agencies as part of this study.

3.3. Study Objectives

3.3.1. Primary Objective(s)

To evaluate the safety and performance of the device by collection of images and associated data using the 3.0T Neonatal MRI investigational device that demonstrates the feasibility of use in clinical neonate and infant populations.

3.3.2. Secondary Objective(s):

To collect per-subject image quality, usability, workflow, and transport data.

To collect usability information for each device configuration (per *MR Procedure Document*).

To optimize device use and configurations, including software and hardware components, functionality with MR accessories, and performance factors.

3.3.3. Exploratory Objectives:

To record per-subject information, including clinical and demographic data.

To collect image data related to clinical follow-up conducted (if applicable) for engineering and device optimization purposes.

3.4. Study Endpoints

3.4.1. Primary endpoints

For both Phase 1 and Phase 2, primary endpoints will be recorded as:

- Collection of MR images and associated data per quotas (Section 5.1.1 - Quotas by Anatomic Region)

- Performance will be determined by summary proportions of images determined to be of evaluable or non-evaluable diagnostic quality
- Safety will be determined by summary rates of adverse events

3.4.2. Secondary endpoints

- MR image quality evaluation(s), per-phase as follows:
  - *Phase 1 and 2* (all subjects): Overall image quality rated on a 1-5 Likert scale
  - *Phase 1* - Qualitative evaluation and optimization (Summary Report) provided by PI, as per applicable *MR Procedure Document*
  - *Phase 2* – Evaluations as described in the *MR Procedure Document*
- Per-subject Transport and swaddling times and data
- Per-subject workflow and transport information
- Per-subject formative and summative usability information (Appendix F – Example 3.0T Neonatal MRI Investigational Device User Experience Questionnaire, Appendix G – Example of Single-Use Disposable Swaddle System User Experience Questionnaire)
  - *Phase 1* – Collected as on-site Sponsor or study staff observations

    (may be completed by Sponsor staff trained on the study protocol and/or onsite study staff)
  - *Phase 2* – Collected by on-site assessments by the scan operator

    (must be completed by trained site study staff)
- Number and type (as determined by Sponsor engineering representative based on investigator device complaint reports) of device issues, as follows:
  - Technical Issues (caused by operator error)
  - Malfunctions (device did not perform as intended)

3.4.3. Exploratory endpoints

- Per-patient medical conditions, information, and demographics, as described in the procedure sections
- *Phase 1 only* – Engineering/optimization images and associated image data from clinically indicated MRI follow-up for unexpected findings

4. DESIGN OF RESEARCH STUDY

4.1. Type of Research Study

4.1.1. Study Type

This is a two-phase, single-site, open-label, prospective research study involving human neonate and infant subjects. This study is designed as a two-phase clinical trial with a feasibility and optimization phase (Phase 1) and controlled image collection study (Phase 2)

Phase 1 is being conducted to optimize and calibrate the device for subsequent data collection in Phase 2 of this study. Both parts may be used for regulatory submission purposes, including CE mark and submissions to other global regulatory authorities in other countries.

Open-Label	☒	*All MR scan configurations are known to researchers and subjects*
Blinded	☐	
Double-Blinded	☐	
Single-site	☒	*There is one investigational site*
Multi-site	☐	
Randomization Procedure	☐	
Not randomized	☒	*Randomization is not required, as there is no comparative hypothesis testing*
Single arm	☒	*There are no comparison or control groups*
Comparator	☐	
Parallel	☐	
Crossover	☐	
Prospective	☒	*Subjects are enrolled and then undergo study procedures*

4.1.2. Rationale for Two-Phase Study Design

This study is being conducted in two phases, as follows:

Phase 1: The first phase (Phase 1) is a feasibility and optimization assessment that cannot be conducted in any other population and is designed to allow collection of clinical image and associated data as well as to assess image quality, workflow, and usability in human subjects. The results from Phase 1 will be considered in deciding whether to continue to Phase 2 and, if Phase 2 is conducted, the most appropriate device configuration. Phase 1 data is not primarily intended for regulatory submission but may, if determined necessary by the Sponsor, be disclosed to regulatory authorities in support of regulatory submission.

Phase 2: Phase 1 will be followed by a sequential second phase (Phase 2) to collect human images and data intended to as sample images and associated per-subject data for use in regulatory submissions.

Images and data from both Phase 1 and Phase 2 may be used to support future engineering activities.

4.2. Controls and Minimization of Bias

The following bias control methods are being employed in this study:

a. Selection bias will be limited by consecutively enrolling subjects meeting the inclusion/exclusion criteria

b. Spectrum bias will be limited by using a population expected to be representative of the general population at the investigational site, without regard for gender, race, or ethnicity.

c. Reader bias will be limited by ensuring that evaluators and readers making performance assessments are separate radiologists (not the PI or neonatologist).

5. STUDY SUBJECTS

5.1. Number of Subjects

Subjects will be enrolled in two phases, to achieve thirty (30) datasets in Phase 1 (Feasibility and Optimization) and up to five (5) datasets in Phase 2 (Data Collection) for a total of thirty-five (35) total evaluable datasets in both phases.

To achieve the target of 35 datasets, a total maximum of 60 subjects may be enrolled per the sample size calculation shown in Section 8.1.1 – Sample Size Determination. The minimum number of patients possible will be used to achieve the target number of evaluable datasets.

5.1.1. Quotas by Anatomic Region

The expected 35 evaluable datasets required for this study are set forth in the quota detailed in Table 2 by anatomical region. There is only one anatomical region for this study.

Table 2- Number of evaluable image datasets

Anatomic Region	Approximate number of evaluable datasets required (*n*)	
	Phase 1 (Feasibility and Optimization)	Phase 2 (Data Collection)
Neurological (Head/Neck/Spine)	30	5

* *n* = approximate total number of evaluable datasets

The Sponsor may choose to end either Phase of the Study when adequate datasets are achieved, based on determination made by the Sponsor. Any such determination that would limit enrolment within a phase and/or individual quota group will be communicated in writing to the investigational site. Any such limitations that apply only within a single quota group do not constitute termination of the study.

5.1.2. Special Considerations for Enrolment

The following special considerations apply to subject enrolment in both Phase 1 and Phase 2.

1. **Incomplete Datasets**: Datasets may be incomplete due to factors such as noise, sequence failure, or patient movement. Datasets determined to be incomplete or non-evaluable by the investigator will not be counted towards the total required datasets for the purposes of determining quota fulfilment (per protocol population), but these will be reported in the total patient enrolment in the study final report

(intent-to-treat population). Both complete and incomplete images and data will be stored and provided to the Sponsor for engineering purposes.

2. **Changes to Quota Requirements during the Study**: The Sponsor reserves the right to change quota or Phase dataset number requirements at its discretion and for any reason within the set patient enrolment maximum. The Sponsor will notify the investigational site in writing of any changes in enrolment quotas.

5.2. Subject Population

Viable neonate and/or infant subjects that meet the inclusion and do not meet the exclusion criteria will be enrolled.

5.3. Protection of Vulnerable Subjects

5.3.1. Vulnerable Subjects

This study involves a vulnerable population (viable neonates and infants), per ISO 14155:2011 that defines a vulnerable subject as any individual 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. This definition includes children, such as the neonates and infants included in this study, which would otherwise require consent from a legally authorized representative acting in their best interests.

This study is being conducted to collect images and data on a device intended for use in neonates and infants that could not be otherwise conducted without using this vulnerable population. The Sponsor has conducted previous internal testing using phantoms to evaluate the safety of the device for use on humans.

Protection of these vulnerable subjects is imperative and the following safeguards will be employed:

a. Only viable, living neonates and infants will be included in this study;

b. No neonates of uncertain viability or nonviable neonates will be included in this research;

c. Individuals engaged in the research will have no part in determining the viability of a neonate, and all such determinations will be made according to the standard clinical practice at the investigational site.

5.4. Inclusion Criteria

Subjects will be included that are:

1. Currently admitted for treatment or observation at the investigational site at the time of enrolment;
2. In the weight range less than 5.0 kg (<5.0 kg[1]) and more than 0.5 kg (>0.5 kg[2]);
3. Viable neonates (birth to 1 month of age) or infants (>1 month to two years of age);[3]
4. Able to safely undergo an MRI scan, as determined by medically qualified personnel;

[1] <5.0 kg is considered equivalent to <5000.00 g
[2] >0.5 kg is considered equivalent to <500.00 g
[3] 1 month is considered equivalent to 30 days; 2 year is considered equivalent to 729 days or less

5. Have parent(s), guardian(s), or legally authorized representative(s) willing and able to provide written informed consent for the subject's participation;
6. Are of appropriate size and shape to fit into the bore of the magnet, inclusive of all monitoring equipment, if any, necessary for the subject's routine clinical care based on standard of care measurement methods, in accordance with site policies :
    a. Maximum width (shoulder-to-shoulder measurement) less than eighteen (18 cm).
    b. Maximum length (head-to-foot measurement) less than sixty (60) cm.

5.5. Exclusion Criteria

Subjects will be excluded that:

1. Have parent(s), guardian(s), or legally authorized representative(s) that require that they accompany the subject into the MR environment that have contraindications to the MR environment or would otherwise be put at undue risk or discomfort, as determined by medically qualified personnel;[4]
2. Have any ferrous or electrical items or non-removable medical devices that are not compatible with MR scanning (including devices labelled as MR Unsafe, MR conditional for which the scanning conditions are not met, or without MR safety labelling that does not satisfy site MR safety requirements) that may pose hazards in the MR scanning or MR environment, in the opinion of the Principal Investigator or medically qualified personnel in accordance with the site's MR Safety policy;
3. Have any contraindications or could otherwise be expected to experience detrimental effects to safety, well-being, or medical care, as determined by the Principal Investigator or medically qualified personnel in accordance with the site's MR Safety policy;
4. Require any scheduled standard of care procedures that are expected to be adversely impacted by participation in this study, in the opinion of the principal investigator or medically qualified personnel; and
5. Have been previously enrolled AND undergone any study procedures under the current study protocol (i.e. the same subject cannot undergo study procedures, including swaddling and/or MR scanning, more than once).

5.6. Screening Subjects for Enrolment

5.6.1. Subject Recruitment

Subjects that are expected to meet the site's MR Safety Policy criteria and any additional supplemental safety policies criteria recommended by the investigator (as per the exclusion criteria) and are otherwise eligible for inclusion will be recruited through a neonatologist, neonatologist fellow, or study staff authorized through written delegation at each investigational site, in accordance with EC/IRB policy.

[4] If it is not safe for the parent or guardian that wishes to accompany the subject into the MR environment, the parent or guardian may opt not to accompany the subject. In this case, the subject would not be excluded. Subjects would be excluded if it is determined to be potentially unsafe for a parent or guardian to accompany a subject into the MR scan suite, and the parent or guardian is not willing to allow the subject to be scanned alone while he/she waits in another area of the hospital.

5.6.2. Screening for Enrolment

Potential subjects will be identified by the Principal Investigator or other qualified site staff. Informed consent will be obtained for those subjects who agree to participate in the study. Subjects will then be screened for enrolment to ensure the subject is eligible to participate per the inclusion/exclusion criteria, as per the judgement of medically qualified personnel.

Subjects who do not qualify based on inclusion/exclusion criteria will be considered screen failures.

Once a subject is determined to be eligible per the inclusion/exclusion criteria including providing written informed consent, the subject will be considered enrolled and assigned a subject number.

5.7. Duration of Enrolment

The study plans to enrol patients for approximately 24 months.

6. PROCEDURES FOR RESEARCH STUDY

6.1. General Procedures

6.1.1. Quality Control Scans

The study staff conducting the investigational MR scans (scan operator) will conduct regular Quality Control scans using phantom imaging according to the MR system Operator Manual. The results of Quality Control scans will be stored at a secure location at the investigational site and may be reviewed by the Sponsor.

Phantom Scanning

The investigator and/or Sponsor representatives may execute phantom scans that simulate human scanning for the purposes of training, troubleshooting, or other engineering optimization purposes at any time during the study.

Specific Absorption Rate (SAR) Scans

The device is equipped with a predictive SAR model designed to conservatively limit actual SAR exposure in research subjects. The predictive SAR model used on the system is detailed in the technical documentation for the Neonatal MRI device. Each scan session will include sequences designed to generate a range of actual SAR data, which is stored in system logs and subsequently collected by Sponsor engineering representatives. Throughout the study, system log files containing experimentally generated SAR data will be routinely collected, along with relevant clinical data such as patient weight (*as described in subsequent protocol sections*), necessary for future evaluation of the system's predictive SAR model versus actual clinical data in the infant/neonate population.

MR Scan Session Log

In order to account for all MR scan sessions using the investigational MR system, the scan operator will maintain a daily *MR Scan Session Log*. Because this investigational MR scanner may be used for concurrent research protocols, the *MR Scan Session Log* (Appendix E–

Example of MR Scan Log) may also contain entries from other approved studies. For this study, the log will include:

a. the GEHC-issued study number,
b. subject number,
c. date of imaging
d. MR Procedure Document version number, in applicable
e. anatomy imaged
f. comments, if applicable

The log will continue as long as the investigational MR device is housed at the site, and will only be discontinued when all EC/IRB-approved studies are completed and the investigational MR device(s) is/are removed from the investigational site.

Note: All human scans for this study, scans done for any other active EC/IRB-approved studies using this device, and other non-clinical scans (i.e. phantom scans for research, service/maintenance, or training) will be logged. This is done so that the log is consistent with the internal log inside of the system for engineering purposes. The log may contain other columns required by other concurrent protocols and some fields may be marked as not applicable (N/A) for other concurrent protocols.

6.2. Phase 1 (Feasibility) and Phase 2 (Data Collection)

Phase 1 of the study will be conducted to collect feasibility data and optimize the MR system. Throughout the term of the Study, the Sponsor will communicate with the PI and Study Staff as required for device optimization. The Sponsor will provide *MR Procedure Document(s)* to the site, and the PI or delegate will complete and return a qualitative *Investigator Summary* within approximately 3 business days after the procedures described in the current MR procedure document have been completed. The Sponsor may provide additional sequentially numbered *MR Procedure Document* versions (numbered as Version 1.0, 2.0, 3.0, etc.) iterative adjustment the procedure for subsequent MR scanning.

Phase 2 will be conducted to collect sample images and associated data for regulatory submission. While hardware and software may be modified throughout Phase 1, a fixed hardware and software configuration will be used for all Phase 2 scanning. Based on the results of Phase 1, *MR Procedure Document(s)* will be provided to the site and used consistently in all Phase 2 scanning.

During both phases, remote TVA connectively feature will be available to scan operators for the purposes of training, troubleshooting, and real-time image quality optimization during phantom and clinical procedures. The TVA feature limits remote connectivity so that no scanning can be initiated without scan operator confirmation.

6.2.1. MR Procedure Documents

At the beginning of the study (prior to initial scanning) the Sponsor will provide an initial *MR Procedure Document* to the site and, as determined necessary by the Sponsor, additional *MR Procedure Documents* will be provided. Study procedures will continue under the documented *MR Procedure Document* until a new *MR Procedure Document* is provided by the Sponsor. During both Phase 1 and Phase 2, the *MR Procedure Document* version used will be documented on each Subject's Case Report Form (CRF).

Sponsor-prepared *MR Procedure Documents* will include the following items:

- *MR Procedure Document* version

- Date of Document
- Estimated number of subjects that will be subject to a particular MR Procedure Document.
- Comments/Specific Instructions for procedures to be performed
    - Additional Sponsor-Requested Assessments of performance characteristics on a 1-5 Likert Scale[5], which may include:
        - Assessments of performance
        - Overall image quality
        - Image contrast
        - Artefacts
        - Fat/water homogeneity
        - Signal-to-noise ratio (SNR)
        - Reconstruction software performance
        - Optimization of application packs (pulse sequence and post-processing software)
        - Usability
        - And/or other assessments

    Note: The investigator is responsible for completing only the assessments indicated by the current version of the *MR Procedure Document*. The investigator should ensure that all study staff completing assessments are aware of any changes.
- Effective Date that the specified study procedures should begin (i.e. begin on or after this date)
- Name and signature of Sponsor Engineering Representative
- Name and signature of Sponsor Clinical Affairs Project Manager

Each *MR Procedure Document* will be assigned a unique, consecutive numerical, Version number (e.g. 1.0, 2.0, 3.0, etc.).

No human MR scanning for this Study will be conducted outside of a Sponsor-authorized *MR Procedure Document*. Phantom scanning may be conducted for training and maintenance purposes without a MR Procedure Document. Scanning that is not compliant with *MR Procedure Document* will be considered a deviation and will be reported according to Section 9.1 – Management of Protocol Deviations.

[5] Likert Scale of 1-5, where:
1 = Very Poor
2 = Poor
3 = Neutral
4 = Good
5 = Excellent
Note: For image quality assessment, scores of 3, 4, or 5 will be considered diagnostic quality, and scores of 1 and 2 will be considered non-diagnostic quality.

6.2.2. Qualitative Investigator Summary (*Phase 1 only*)

The PI will complete an qualitative *Investigator Summary* (Appendix A– Example of Investigator Summary Document) documents within approximately 3 business days of completion *MR Procedure Document*. The Qualitative Investigator Summary will include:

- Consecutively numbered Investigator Summary Number
- Version number of *MR Procedure Document(s)* being discussed
- Qualitative Comments related to results
- Comments/Suggestions for optimization of future study procedures (i.e., workflow, scanning, usability)
- PI or delegate's name, signature, and date completed

All completed *Investigator Summaries* will be submitted by the PI or delegate to the Sponsor's *Clinical Affairs Project Manager*, who will sign and date each document to confirm receipt and store a copy of the document in the Sponsor's Clinical History File (CHF).

6.3. Per-Subject Procedures

6.3.1. Pre-MR Scanning Activities

MR Pre-Screening

To verify that subjects with necessary medical equipment present can safely fit into the study device bore with normal airflow and without contact, subjects will be verified to be of acceptable size for study MR scanning using the Sponsor-provided sizing tool ("horseshoe" shaped ring) with necessary attached medical equipment prior to removal from the normal clinical care environment.

> **Note**: The sizing tool is a study device that may only be used after written informed consent for participation has been attained.

The study staff will then ensure that the subject and any person(s) accompanying him or her into the MR environment satisfy all applicable site MR Safety Screening requirements.

If the subject is determined not be of appropriate size, not to meet MR Safety Screening policies at the site, or is discharged from clinical care at the investigational site prior to MR scanning, the subject will be withdrawn from the study.

Duration of Active Enrolment (for AE/SAE reporting purposes)

Subjects may be transported to the MR suite before or after removal from their incubator, crib, or other standard of care bedding.

Subjects will be considered actively enrolled (for AE/SAE reporting purposes) in the study on a per-subject basis from the time that the Sponsor-provided horseshoe-shaped sizing tool is used to measure subject size (the first study procedure of MR Pre-Screening). It is mandatory that the sizing ring is used for all subjects before other study procedures to ensure that the subject is of proper size for the MR bore.

Active enrolment will be considered to end on a per-subject basis upon the later of:

a. The time that the subject is returned to his or her standard of care clinical environment and all Sponsor provided devices are removed from the subject, including Sponsor-provided swaddle, protective padding, and all other study devices.

b. After active enrolment ends, images and data about any standard of care follow-up or other medical care resulting from unexpected findings may still be accessed observationally and collected by the Sponsor for research purposes.

Pre-Study Feed and Sleep Procedures

Per the applicable standard of care procedures required at the investigational site, each participating neonate or infant subject will be allowed adequate feed and sleep to ensure minimum disruption of care during MRI scanning, as follows:

a. The subject will be either breast or bottle fed by or in the presence of the parent/legal guardian.

b. The subject will be placed in a position that is relaxed and comfortable, with the expectation that it will be reasonably possible for the subject to sleep through the MRI scan.

Swaddling Subjectsand Use of Protective Padding

If used, unique identification number of the Sponsor-provided single-use disposable swaddle will be documented and noted on the swaddle log (Appendix C – Example of Single-Use Disposable Swaddle Log), and the following data will be collected during swaddling:

- Was a Sponsor-provided swaddle used (Y/N). If no, explain why not.
- Was other hospital-provided swaddling (e.g., blankets) used (Y/N); explain why
- Swaddle ID number
- Time of subject placement in the swaddle (on 24 hour clock)
- Swaddled shoulder circumference (in either swaddle or other padding)
- Shoulder-shoulder length before swaddling
- Description of when swaddling occurred (e.g., diapering, bathing, feeding or changing, etc.)
- Was backboard used (Y/N). If yes, explain why used

Subjects should be placed into the Sponsor-provided swaddles by trained study staff according to the instructions provided by the Sponsor. Subjects may be placed in the Sponsor-provided swaddles either immediately before transport to the MR suite or at an earlier time that will minimize subject discomfort, such as during routine feeding, bathing, or diapering. Efforts should be made to place subjects in the Sponsor-provided swaddles as close as possible to the time of MR scanning unless this presents a potential hazard or undue discomfort to subjects. If a swaddle is not used, the subject should be snuggly placed in blankets provided by the investigational site, as such to prevent direct contact between the subject and the walls of the 3.0T Neonatal MRI investigational device (the bore) during scanning.

The site should follow the Sponsor's operator manual for specifications and application of padding to the subject prior to scanning, and padding provided by the Sponsor should be utilized for all subjects. At the discretion of the Principal Investigator or medically qualified delegate, the site may also apply necessary additional site-provide padding along with Sponsor-provided padding.

General Method for Recording Temperature

Subject body temperature will be recorded at defined intervals before, during, and after scanning as detailed in the following sections. In the MR suite and during scanning, MR Safe Invivo Expression monitors should be used to determine temperature and other vital signs.

Pre-Transport Subject Information

The following pre-scan session subject information will be recorded for all subjects:

- gender
- age since birth (days for subjects aged ≤30 days and months for subjects aged >30 days)
- gestational age (for subjects ≤30 days old)
- infant or neonate status (neonate = birth to ≤30 days; infant >30 days to <2 years)
- *Pre-transport temperature* body temperature just before leaving the incubator or crib, measured according to the standard clinical practice at the investigational site as follows:
    - temperature measurement value
    - device type (record standard of care device), and
    - anatomical area of measure (specific area of skin surface)
- head circumference
- weight on day of scan
- Additional Sponsor-Requested Assessments:
    - Blank areas will be included for these assessments (10 blank "Assessment Title" lines with associated 1-5 Likert scales) will be provided on the CRF to accommodate Sponsor-requested elements that may be specified for each *MR Procedure Document*. The investigator is responsible for being aware of any additional elements required by each *MR Procedure Document* version number. The investigational site(s) will be notified of any additional instructions for completing comments, and will be responsible for completing the comments field as instructed after appropriate training and instruction has been provided by the Sponsor.
- Investigator comments
    - The investigator is encouraged to make additional comments on any atypical or exceptional conditions of the subjects, including but not limited to pertinent medical history or known deformity.

Pre-Scan Subject Transport

The subject will be transported to the MR suite either before or after swaddling (whichever is less disruptive to the subject's care, in the opinion of the study staff) from his or her standard clinical care environment. The following parameters will be recorded about subject transfer to the MR scanning location:

- Transport mode into MR suite (subject moved by incubator/crib to MR suite or subject moved by transport cart/table)
- Time of removal from incubator/crib (on 24 hour clock)
- Number of staff required to transfer (departing incubator/crib; arriving MR)

The transfer table will be docked to the MR scanner and advanced to centre the anatomy of interest (known as "land-marking") relative to the MR scanner. Transport is considered to end when the table is docked and the subject is advanced into the magnet bore.

Pre-scan Environmental Condition

Immediately prior to the first scan series, the following environmental conditions in the MR scanning room will be recorded:

- Scan room temperature
- Number of personnel required to transport the MR table from the MRI preparation room into the scan room, dock the cart/table to the MR scanner and position, land-mark, and advance the subject into the magnet bore

Protective Devices/Procedures

All subjects require mandatory hearing protection that provides a minimum of 22 dB attenuation prior to MR scanning (ear plugs or a combination of ear plugs and ear muffs, in accordance with site MR Safety Polices).

Use of the horseshoe-shaped sizing ring to verify that subjects can safely fit into the bore of the MR device is mandatory immediately prior to scanning.

The scan operator or delegate will ensure that the subject meets the criteria for MR scanning according to the site MR Safety Policy. In addition, the study staff may screen subjects and accompanying person(s) for presence of ferrous metallic objects using a hand-held metal detector, under the direction of the principal Investigator or delegate. If new information shows that the subject does not meet the site MR Safety Policy requirements, the subject will be withdrawn.

In neonate and infant populations, special care should be taken to check umbilical or limb security devices that may have metal parts that are not safe for MRI scanning. Check if the infant or neonate has any umbilical clips or name bands with metal parts for MR safety before entering the MRI suite; remove them if deemed MR unsafe and it is safe to remove these per the standard clinical practice at the site. Special care should be taken to remove all metal objects from subjects and persons accompanying the subject prior to initiating MR scanning. If objects or devices that are not safe for MRI scanning are not able to be removed safely, the subject should be withdrawn from the study.

Protective padding shall be used on all subjects according to the device's operator manual and it is preferred that the Sponsor-provided protective padding is used. If the site uses site-provided protective padding for a particular subject, the reason for not using the Sponsor-provided protective padding will be documented.

Preparation for Scanning

Immediately before initiating the scan, ensure that the Expression Monitor (Invivo) is connected and monitoring vital signs, including but not limited to body temperature and O_2 saturation. Once acclimated to the scan environment, the following scanning information shall be recorded by the scan operator, including the following:

- *Pre-scanning baseline temperature*: body temperature measurement made with Invivo Expression Monitor (Invivo), as follows:
    - the time (minutes) allowed for acclimation once in the magnet bore before taking the temperature measurement
    - temperature measurement value
    - anatomical area of measure (specific area of skin surface).

The study staff will set the alarm level on the Expression Monitor (Invivo) to trigger at 0.5°C above the pre-scanning baseline temperature.

6.3.2. MR Scanning Procedures

Monitoring Subjects during MR Scanning

During MRI scanning, subjects will be monitored in real-time using a properly functioning Expression MRI Patient Monitor (Invivo, Corp; Orlando, FL, USA). The subject will be observed all times during the MR scan by a qualified medical professional (nurse, neonatologist, and/or other medical doctor qualified for neonatal/infant care) on the study staff who shall remain in the magnet room with the subject during scanning. The observing staff should remain in a position where they can readily observe the subject and monitor and, if necessary, contact the scan operator during the scanning session.

A conservative threshold for body temperature alarm is selected, as such that body temperature change is sufficient to trigger an alarm (0.5°C above the pre-scanning baseline temperature) is not in itself considered a clinically significant risk to patients; these patients will be evaluated by a medically qualified member of the study staff for any other possible signs or symptoms and they will determine whether an AE has occurred as per the standard procedures described in Section 11 – Complaint Handling and Adverse Event Reporting.

If a body temperature alarm on the monitor is triggered at any time during scanning, the study staff should stop the scan series. Then, the following elements will be documented as part of study data for each such alarm occurrence:

- the time of alarm
- *Alarm Temperature*: the body temperature at time of alarm, based on body temperature measurement made with the Expression Monitor (Invivo), as follows:
    - temperature measurement value
    - anatomical area of measure (specific area of skin surface).
- the time it takes to return to pre-scanning baseline temperature (minutes/seconds)

Note: In the event that the baby's body temperature does not return to a level at or below the pre-scanning baseline temperature within the study's scanning period (not to exceed 60 minutes from first localizer to end of scanning) patient scanning will be discontinued (if collected, the patient's data collected up until this time may still be used for study purposes, and post-scanning information may still be recorded about the patient).

- any conditions observed that possibly contributed to temperature rise, such as swaddling, environmental conditions, distress, or scanning conditions? (Y/N, if yes explain)
- decision to continue the scan session (do not continue after first alarm)? (Y/N)
- *Continuing Temperature*: the body temperature at the time of scanning was continued using an Expression Monitor (Invivo), as follows:
  - temperature measurement value
  - anatomical area of measure (specific area of skin surface).

A medically qualified investigator should evaluate each patient to determine if it is safe to continue scanning once the patient's body temperature returns to pre-scanning baseline temperature or lower in the event of an alarm. If an alarm is triggered more than once during a single scan session, scanning will be discontinued. If collected, the patient's data collected up until this time may still be used for study purposes, and post-scanning information may still be recorded about the patient.

Subject MR Scanning Procedures

The total time starting from the start of the first localizer to the time at the end of the last scan will not exceed sixty (60) minutes. Additional time may be required for setup and removal of the patient.

The scan operator will:

a. enter the subject's anonymized ID number in the "Subject Name" and "Subject ID" field in the MR scanner's user interface.

b. enter the subject's weight in the MR scanner's user interface.

In addition to the scan operator, a member of the study staff cleared to enter the MR magnet room will remain in the MR suite at all times when a subject is present in order to assist the scan operator should an emergency situation arise

MR Scanning Information

For each scanning session, the following scanning information shall be recorded by the scan operator, including the following:

- *MR Procedure Document* Version Number
- Phase of Scanning (Phase 1 or Phase 2)
- Subject number
- Date of scanning
- Was the subject sedated for standard of care reasons prior to scanning (Y/N)
- Time and type of clinically indicated sedative administration

  Note: No sedatives will be administered for the purpose of this study. Check yes only if the subject was previously administered clinically indicated sedative(s) within the last 24 hours prior to scanning.

- Start and End time of scanning, determined by time just prior to first localizer and time at end of last scan (on 24 hour clock)

- Scan operator name and signature
- Anatomy scanned (i.e. neurological (head/neck/spine) Was subject fed before (<1 hour) prior to scanning? (Y/N)
- Did subject require pacifying during scan? (Y/N) Were there any repeat scans done due to motion artefacts caused by subject voluntary motion? (Y/N)
- Were there any recoverable system errors or failures during the scanning session? (Y/N) If Yes, please describe.
- Comment: Describe any image features which may have negatively affected the image quality including items such as, but not limited to, artefacts, tissue contrast, noise etc.
- Additional Sponsor-Requested Assessments
    - Modifiable CRF fields (10 blank "Assessment Title" lines with associated 1-5 Likert scales) will be provided on the CRF to accommodate Sponsor-requested elements that may be specified for each *MR Procedure Document*
        - The investigator is responsible for being aware of any additional elements required by each *MR Procedure Document* version number.
        - The investigational site(s) will be notified of any additional instructions for completing comments, and will be responsible for completing the comments field as instructed after appropriate training and instruction has been provided by the Sponsor.
- Investigator Comments
    - The investigator is encouraged to make additional comments on any atypical or exceptional events that occur during subject scanning.
    - During the study, the Sponsor may provide additional instructions for recording specific types of conditions or information in the comments field at its discretion as part of an *MR Procedure Document*
    - The study staff will be responsible for completing the comments field as instructed in the applicable *MR Procedure Document* (indicated by version number) after appropriate training and instruction has been provided by the Sponsor.

In Phase 1, the Sponsor's engineering representative, if present, may optionally record any applicable comments on a dedicated CRF page.

MR Scanner Issues

Issues that occur during the scanning session: In the event of recoverable issues during the scan session:

a. the scan operator will generate an issue report according to the instructions provided by the Sponsor,
b. Data may be collected from the MR scanner by the Sponsor's authorized engineering representative.

Note: Any Sponsor engineer involved at the site will be trained on the clinical protocol. These Sponsor engineers are qualified to answer technical questions about the device, but will not be authorized to provide training, retraining, or answer study conduct questions raised by

study staff, such as issues with informed consent or other protocol issues/questions. Study conduct questions that are non-technical in nature should be referred to the Clinical Affairs Project Manager. Device use, installation, operation, maintenance, and other technical questions may be addressed with on-site engineers.

Non-recoverable malfunctions: Non-recoverable malfunctions will be considered those that are not resolved by the scan operator rebooting/resetting the system. In the event of a non-recoverable MR system malfunction:

a. the scan session will be stopped,
b. the subject will be removed from the MR environment and returned to their standard of care environment,
c. the equipment will be assessed by the Sponsor, and
d. The Sponsor must authorize that the device may be used prior to scanning additional clinical subjects.

6.3.3. Post-scanning MR Procedures

Post-scanning Subject Information

Post-scanning information will be recorded for all subjects:

- *Post-scanning temperature*: Body temperature, immediately before removal from the MR scanner (post-scan body temperature), body temperature measurement made with an Expression Monitor (Invivo) and anatomical area of measure (specific area of skin surface).
- *Final temperature*: Body temperature measured after transport and just before the subject is placed into the routine care environment, as follows:
  - temperature measurement value
  - device type (record standard of care device), and
  - anatomical area of measure (specific area of skin surface)

  Note: It is preferred that the same method as used for the *Pre-transport Temperature*
- End of Enrollment Time: Time when the patient is returned to the clinical care area and all Sponsor-provided device components (i.e., Swaddle, Invivo monitor, pads, etc.) have been removed from the subject.
- Additional Sponsor-Requested Assessments
  - CRF fields (10 blank "Assessment Title" lines with associated 5-Likert scales) will be provided on the CRF to accommodate Sponsor-requested elements that may be specified for each *MR Procedure Document*.
    - The investigator is responsible for being aware of any additional elements required by each *MR Procedure Document* Version number.
    - The investigational site(s) will be notified of any additional instructions for completing comments, and will be responsible for completing the comments field as instructed after appropriate training and instruction has been provided by the Sponsor.
- Comments
  - The investigator is encouraged to make additional comments on any atypical or exceptional events that occur during subject scanning. During the study, the Sponsor may provide additional instructions for recording specific types of conditions or information in the comments field at its discretion as part of

an *MR Procedure Document*. The study staff will be responsible for completing the comments field as instructed in the applicable *MR Procedure Document* (indicated by version number) after appropriate training and instruction has been provided by the Sponsor.

Post Scan Environmental Conditions

At the end of the last scan series when the scan operator enters the scan room to remove the subject from the MR device, the scan operator will record:

- Scan room temperature
- Number of personnel required to remove subject from the scanner and undock the cart/table from the MR scanner and transport the MR table out of the scan room and into the MRI preparation room.

Post Scan Operator Assessments

For each subject, a designated study staff member present during the MR scan session will complete the usability survey for all applicable device components (Appendix F – Example of 3.0T Neonatal MRI Investigational Device User Experience Questionnaire; Appendix G – Example of Single-Use Disposable Swaddle User Experience Questionnaire). More than one study staff may collaborate to complete these surveys, but only one survey form should be completed based on the consensus between all participating study staff. The Sponsor's representative may also collect observational comments during human scanning.

6.3.4. Evaluations

Performance Evaluation

Image sets will be labelled according to subject identification number. Images will be evaluated as evaluable (diagnostic) or non-evaluable (non-diagnostic) by two evaluators, and then evaluable images will be read for image quality by a separate reader, as shown in Figure 2.

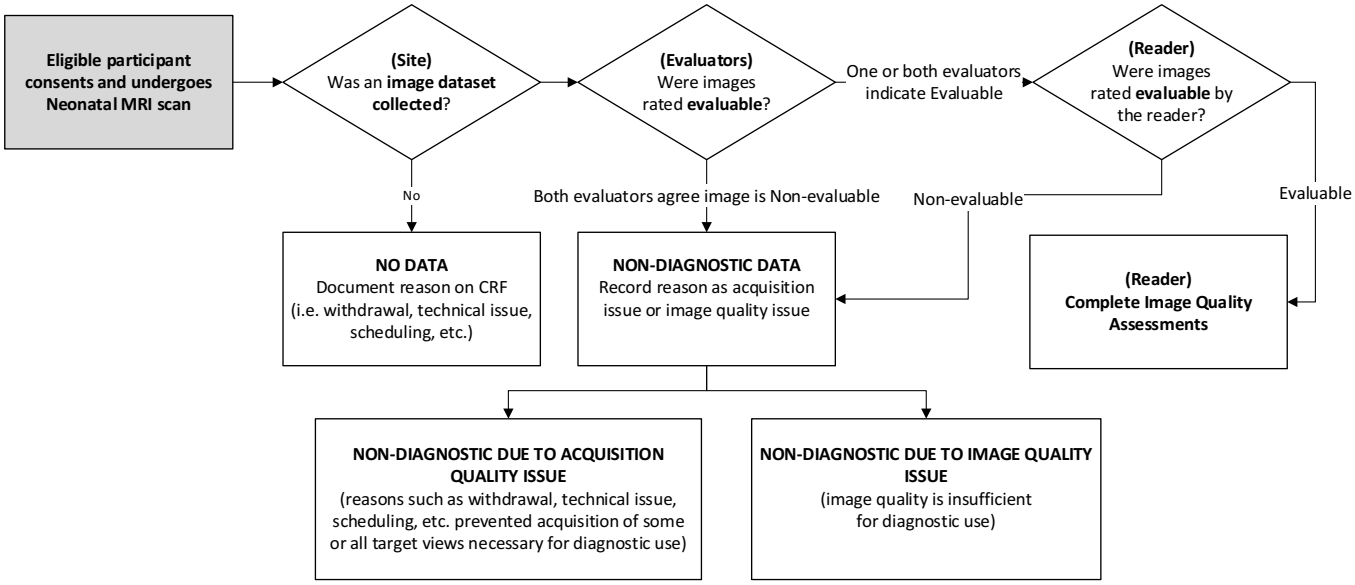


Figure 2 – Flowchart of performance evaluation. Determination of evaluable/non-evaluable for diagnostic purposes will be used as the primary performance measure. All secondary Image Quality Assessments will be descriptively summarized.

MR image datasets for each subject will be evaluated twice by two delegated radiologists serving as image evaluators (Evaluator 1 and Evaluator 2) as:

- Evaluable (Diagnostic Quality) [6], or
- Non-evaluable (Non-Diagnostic quality).

The evaluations and printed name and signature of the image evaluator(s) will be recorded to an Evaluator CRF. In the event that the two evaluators (Evaluator 1 and Evaluator 2) disagree on whether an image is evaluable or non-evaluable, a third medically qualified reader (Reader 1) will arbitrate to provide an evaluable/non-evaluable decision, which will be recorded to the Reader CRF and treated as the final decision for the image set.

Image Quality Assessments

All evaluable images will be further examined by a single reader (Reader 1) that may be the PI or a qualified delegated radiologist for image quality on a 1-5 Likert Scale,[7] as follows:

- Overall image quality

[6] An image set may be considered of diagnostic quality if it contains images suitable for diagnosis (not all images views are typically required to be diagnostic based on specific scanning circumstances, so long as applicable views necessary for diagnosis are present)

[7] Likert Scale of 1-5, where:
1 = Very Poor
2 = Poor
3 = Neutral
4 = Good
5 = Excellent
Note: For image qualityassessment, scores of 3, 4, or 5 will be considered diagnostic quality, and scores of 1 and 2 will be considered nondiagnostic quality.

- Image contrast
- Presence of artefacts
- Signal to noise ratio (SNR)
- Tissue contrast
- Fat/water homogeneity
- Additional Sponsor-Requested Assessments
    - CRF fields (10 blank "Assessment Title" lines with associated 1-5 Likert scales) will be provided on the CRF to accommodate Sponsor-requested elements that may be specified for each *MR Procedure Document*
        - The investigator is responsible for being aware of any additional elements required by each *MR Procedure Document* version number.
        - The investigational site(s) will be notified of any additional instructions for completing comments, and will be responsible for completing the comments field as instructed after appropriate training and instruction has been provided by the Sponsor.

6.4. Unexpected Findings

MR scanning in this study is for research purposes only, and is not intended to diagnose or treat any disease or condition. Furthermore, study images shall not be reviewed or provided for diagnostic or any other purposes which may affect patient care. Study images are not being evaluated for specific clinical findings.

However, in the course of performing study procedures in any part of this study (Phase 1 or Phase 2), should the study staff observe unexpected findings, the Principal Investigator may choose to communicate such findings to the subject's parent(s) or legally authorized representative(s) and/or other clinicians involved in the subjects routine clinical care. A report of an unexpected finding should clearly state that the study MRI scans have been reviewed only for technical purposes as required by the study and are not meant to supplement or replace any clinical MRI exam or MRI report as would be provided for standard of care exams. Further, it should be reported that the study scans were performed on an investigational device which is not yet approved for diagnostic imaging. Thus, any findings described cannot be guaranteed to be accurate or of clinical significance. The study Principal Investigator may note details of what is seen related to the unexpected finding to parent(s) or legally authorized representative(s) and/or, if necessary, to other clinician's involved in the subject's routine clinical care, but no diagnosis should be rendered based on study data. The study Principal Investigator may make recommendations for standard of care imaging follow-up, which, if necessary, will be conducted outside of this study. When an unexpected finding is reported, subjects in this study are then to be managed as patients with regard to standard of care in accordance with the site's policies and procedures.

The Principal Investigator shall complete the study Investigator's Report form regarding unexpected findings, or the noted absence thereof, for every study scan session. The PI may use this form to communicate findings to the responsible clinicians. The form should be stored in the study file, and a copy of the completed form may also be stored in any other location required or recommended by the General Medical Council record keeping guidelines.

6.4.1. Follow-up for Unexpected Findings

In Phase 1 of this study, if unexpected findings identified during this study result in referral for further MRI diagnostic evaluation or other medical care according to the standard of care at the investigational site, de-identified images and associated image data from the standard of care MRI may be observationally collected and provided to the Sponsor for engineering development and device optimization purposes. The occurrence of unexpected findings will be reported on the case report form (CRF). This data is being collected for exploratory engineering development and device optimization purposes, to learn more about performance characteristics and potential artefacts in Neonatal MRI scans. Images and associated image data will be provided at the discretion of the Principal Investigator, and may not be available for all patients with unexpected findings.

6.5. Withdrawal and Discontinuation Criteria

All subjects must be admitted for care in the NICU or other neonatal or infant care department or unit affiliated with the investigational site at the time of enrolment and scanning to be eligible to participate in this study. If a subject is discharged from clinical care at the investigational site prior to MR scanning, the subject will be withdrawn from the study.

The subject's medical care shall take precedence over any imaging or other procedures associated with the study.

If it is determined during the exam that the study imaging will in any way negatively impact required clinical care, the subject shall be immediately withdrawn from the study.

In the event the subject appears to be in pain or undue discomfort, if potentially destabilizing vital signs are observed by visual inspection or via monitoring equipment, or if the parent(s) or legally authorized representative requests to discontinue study procedures, the study procedures will be discontinued immediately and the subject will be removed from study, as determined necessary by the medically qualified staff at the investigational site. The subject shall be removed from the MR environment as soon as safely possible, and, if necessary, care will be provided to the subject to alleviate any discomfort according to the site's standard of care. Data collected up until the time of withdrawal may still be used and disclosed to the Sponsor for research purposes.

The subject's parent or legal guardian may withdraw him or her from study participation at any time, for any reason without consequence.

The study staff 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/IRB should be notified per their notification of subject withdrawal policy.
There shall be no negative repercussions to the subject, parent(s) or legally authorized representative, or Study Staff for deciding end any study procedures.

6.6. Study Flowchart

Table 3– Flowchart detailing the data elements to be collected during each part of the study

Procedure/ Data Element	General Procedures (time interval)	Recruitment / Screening	Pre-Scan	MR Scanning	Post-Scan	Reader/ Evaluator Assessments
Quality Control Scan	Sponsor-set interval(s)[1]					
Specific Absorption Rate (SAR) Scans				X		
Running MR Scan Session Log	Daily verification			X		
MR Procedure Documents (Prepared by Sponsor)	Prior to enrolling first subject, thereafter at Sponsor-set regular interval[1]					
Qualitative Investigator Summary (Prepared by PI)	Within ~3 business days of completing MR Procedure document activities				X	
Inclusion/Exclusion		X				
Collect subject Information			X	X	X	
MR Safety (subject and any persons accompanying him or her into scan room)		X	X	X	X	
Application/Removal of Swaddling (if used)/Padding			X		X	
Transport			X		X	
Environmental conditions			X		X	
MR Procedure Document Identification (Version number)				X		
MR Scanning Information				X		
Software/Hardware components used				X (Phase 1 only)[2]		
MR Scanner Technical Issues/Malfunctions				X		
Additional Sponsor-Requested Assessments			X	X	X	X(reader only)

Procedure/ Data Element	General Procedures (time interval)	Recruitment / Screening	Pre-Scan	MR Scanning	Post-Scan	Reader/ Evaluator Assessments
			(defined in MR Procedure Doc)	(defined in MR Procedure Doc)	(defined in MR Procedure Doc)	(defined in MR Procedure Doc)
MR Images and Data				X	X	X (access to)
Evaluable (Diagnostic)/Non-evaluable (Non-diagnostic) Assessment						X (reader and evaluators)
Image Quality Assessments						X (reader only)
Overall image quality (*based on investigator's experience*)						X (reader only)
Image contrast						X (reader only)
Presence of artefacts						X (reader only)
Signal to noise ratio (SNR)						X (reader only)
Tissue contrast						X (reader only)
Fat/water separation						X (reader only)
AEs/SAEs			X (From placement on swaddle, if used, or if not used from removal from clinical care environment to MR)	X	X (to removal from swaddle/padding and return to clinical care environment)	
MR System Errors/Issues				X		
MR Component/Accessories Errors/Issues			X	X	X	
Usability Assessments						
System Usability Scale (SUS)	Operator completes at end-of-scanning for					

Procedure/ Data Element	General Procedures (time interval)	Recruitment / Screening	Pre-Scan	MR Scanning	Post-Scan	Reader/ Evaluator Assessments
	each *MR Procedure Doc* in Phase 1 and at end of Phase 2					
User Experience Scale (UXS)	Operator completes end-of-scanning for each *MR Procedure Doc* in Phase 1 and at end of Phase 2					
Usability for Device Components					X	
Qualitative Investigator Summary	PI or designee completes for each Sponsor-Investigator meeting in Phase 1					
End-of-Phase Summary Report	PI or designee completes at end of Phase 1 and Phase 2					

Note: X = to be conducted in indicated part of the study

1. Conducted at intervals set and determined by the study Sponsor. The PI may also complete additional general quality scans that do not use human subjects (i.e. phantoms) at any time during the study
2. For Phase 1 scanning only; In Phase 2 these components are filled for all subjects by the applicable *MR Procedure Document* Version

7. TRAINING PLAN

7.1. Training Plan for Research Device/Product

Study Staff will be trained on the use of device system, its components, and Sponsor-provided accessories such as the Sponsor-provided patient monitoring equipment. The Sponsor will provide initial instructions for use of the device and swaddles and, as necessary, subsequent training on any changes to the device, including any necessary storage and handling requirements, preparation for use, any pre-scan checks of safety and performance and any precautions to be taken after use, (e.g. disposal).

No training will be conducted on human subjects.

7.1.1. MR Procedure Documents

The PI is responsible for ensuring that all MR scan operators that will be operating the research device will be made aware of and, if necessary, provided training on scanning procedures at the beginning of the study and after any new version of the *MR Procedure Document* is released by the Sponsor to the investigational site.

7.1.2. Configuration Changes

The PI is responsible for ensuring that all MR scan operators that will be operating the research device will be made aware of and, if necessary, provided training on device configuration changes released by the Sponsor to the investigational site.

7.2. Training Plan for Protocol

Study staff will be trained on the Study protocol and Study procedures, including completion of Informed Consent Forms (ICFs), Case Report Forms (CRFs), *MR Procedure Document*, and other study documentation.

Training will also be provided to ensure appropriate storage and handling of images and data. All study staff will be required to be trained on Good Clinical Practice (GCP) guidelines per ISO 14155:2011.

A record of all formal training attendance and date conducted will be stored in the Site Regulatory Binder and provided to the Sponsor for inclusion in the Sponsor's Clinical History File (CHF).

8. DATA ANALYSIS AND STATISTICS

8.1. Statistical Analysis Methods

8.1.1. Sample Size Determination

Based on the literature, studies including low birth weight neonates commonly assume a 20% dropout rate.[28] Compared to gold standard, approximately 82% of images attained from neonates/infants with MRI are diagnostically useful (evaluable),[29] in part due to subject movement during scanning. The enrolment quota calls for 30 (Phase 1) and 5 (Phase 2) evaluable image sets. More than one image set may be collected from a single subject; however, this case is exceptional and may not be common.

This study requires a population (N) such as that:

$$0.82N - (0.82 \times N)(0.2) = (30\ phase\ 1 + 5\ phase\ 2)$$

To satisfy this requirement, a minimum population size of $N = 53$ is required. This is approximated upwards to $N = 60$ to account for unforeseen contributions to dropout or evaluable image rates in sensitive neonate and infant populations. It is prospectively expected that Phase 1 of this study may be ended early if required data for engineering purposes is collected before the maximum number of subjects are enrolled; it is also prospectively expected that Phase 2 of this study may be ended early if required data for regulatory submission is collected before the maximum number of subjects are enrolled in this Phase. Any determination to end the study before the expected number of subjects has been enrolled will be provided by the Sponsor, in writing, to the investigational site.

8.1.2. Statistical Analysis Methods

As necessary to support 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.

8.1.3. Other Analysis Methods

Images and associated data being collected in this study are intended for use on a per-subject basis for engineering purposes.

Upon completion of this study, the Sponsor's authorized research and engineering program may utilize data collected in this study in full or in part for authorized engineering purposes.

The principal investigator (PI) at each site may be asked to provide electronically tabulated data summaries for subject demographics and other descriptive data summarizing study results. PI-prepared data tabulations will not be controlled or verified by the Sponsor. These results are collected for learning purposes only, and any PI-provided data tabulations will be summarized in the final study report for reference only. Any direct or derived results from PI-prepared data tabulations will not be used by the Sponsor for regulatory submissions.

8.2. Interim Analysis

There are no interim cohort-based statistical analyses for this study. At the Sponsor's discretion and per local EC/IRB requirements, the status of enrolment and other subject data may be summarized at any time determined by the Sponsor during this study.

8.3. Handling of Missing Data

The Sponsor may descriptively summarize the primary performance and safety endpoints from Phase 1 and Phase 2 of this study, including the descriptive statistical summary of patients that exhibit a body temperature rise of more than 0.5°C from acclimated pre-scanning baseline body temperature (resulting in an Expression Monitor alarm during scanning). If the Sponsor observed that the dataset for any subject is incomplete, additional clarification from the investigator may be requested. The Sponsor may additionally request copies of any clinical imaging datasets (including MRI scan datasets and other clinically indicated imaging examinations) that are conducted as follow-up to unexpected findings observed in this study.

8.4. Pass/Fail Crteria of the Study

The study will be considered successful if sufficient evidence is collected to inform the performance and safety of the 3.0T Neonatal MRI investigational device in a representative population of neonates and/or infants, in accordance with Annex X of the European Medical Device Regulation.

9. OTHER INTERIM ACTIVITIES (QUALITATIVE INTERIM SUMMARIES)

9.1. Phase 1 Qualitative Investigator Summary

For Phase 1 of this study, the PI is responsible for preparing qualitative Interim Summaries based on meetings between the Sponsor and investigator, as described in Section 9.1. Phase 1 Qualitative Investigator Summary (Phase 1 only).

These documents, along with images and data collected to date, will provide a basis for the Sponsor's determination of *MR Procedure Document*.

9.2. Phase 1 and Phase 2 End-of-Phase Interim Reports

A total of two End-of-Phase Interim Reports will be prepared by the PI at the end of enrolment for Phase 1 and at the end of enrolment for Phase 2. The PI will descriptively summarize the subject population and imaging results collected to date. This may include data tabulations, at the discretion of the PI. The Phase 1 End-of-Phase Interim Report may be considered by the Sponsor in decision-making activities required for Phase 2, and may be summarized in the Sponsor's final clinical study report. PI-prepared data tabulations will not be controlled or verified by the Sponsor. These results are collected for learning purposes only, and any PI-provided data tabulations will be summarized in the final study report for reference only. Any direct or derived results from PI-prepared data tabulations will not be used by the Sponsor for regulatory submissions.

10. DEVIATIONS

10.1. Management of Protocol Deviations

All human MR scanning with the investigational device used in this study must be conducted under a current *MR Procedure Document* version. If any clinical scan procedure is conducted that is not compliant with the current *MR Procedure Document* version it will be considered a deviation and should be reported according to the following guidelines.

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.

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.

11. COMPLAINT HANDLING AND ADVERSE EVENT REPORTING

11.1. Foreseeable Adverse Events and Device Effects

MRI is generally considered safe for adults and babies because it does not involve exposure to ionizing radiation, such as x-rays. MRI of 4T or less is considered non-significant risk for infants and neonates, and population-specific risks are well described.[26,30,31,32,33,34,35] The known risks typically associated with 3T MRI scans in this study are listed below and have been mitigated by the Sponsor to levels that are as low as reasonably practicable (ALARP), to levels equivalent or less than MRI using commercially released scanners:

Movement of Metal Objects: Magnetic fields in MRI can cause internal or external ferrous metal (e.g. implants, umbilical cord clamps, oxygen tanks, infant security bands, scissors, paperclips, and pens) small enough to be innocuous to adults to move or become projectile, leading to minor injuries like cuts/bruises and, in rare cases, serious injury or death.

Thermal Effects: Body temperature can change due to environmental cooling and/or MRI radiofrequency (RF) warming. Typical specific absorption rates (SAR) during study MRI scanning are not expected to cause injury. In rare cases, serious burns can occur that are typically related metallic object presence or improper patient positioning.

Semi-permanent Cable/Device Removal: Chest leads and other semi-permanent attached cables/devices can warm and electronics can function abnormally, potentially causing discomfort, injury, interruption of care, and, in rare cases, serious destabilization. Devices not known to be safe in the MRI environment may be removed or replaced when doing so would not detrimentally impact normal medical care, otherwise the subject will be withdrawn.

Peripheral Nerve Stimulation: Transient skin sensations ('tingling') or peripheral nerve stimulation (PNS) is related to dB/dt and gradient rise time, and is expected to be rare in neonates and infants due to small skin surface area and conservative device thresholds.[26] Subjecting infants to sudden, rapidly changing gradient magnetic fields during imaging can, induce circulating currents in conductive tissues of the body that typically are not painful and resolve spontaneously, though, in theory, discomfort or pain from PNS in infants is possible.[26]

Acoustic Noise: High noise levels in the scan room and in the bore of the scanner during MRI scanning may cause discomfort but are not normally hazardous with proper hearing protection. Spontaneously resolving hearing loss/tinnitus typically related to improper hearing protection can, in rare cases, become chronic or severe. Hearing protection

(combination of earplugs or ear plugs combined with earmuffs to achieve noise reduction of ≥22dB is mandatory during MRI in this study)

Adverse Effects due to Delay of care: Though discontinuation of study procedures for urgent medical care is not anticipated, unexpected urgent care may be delayed due to removal from the MRI or other study devices. The expected delay is only a few minutes, but there is a risk that any amount of delay could detrimentally impact urgent medical care.

In addition, there are possible, but not anticipated risks that have been identified for the Neonatal MRI device during development. These risks have been identified and mitigated to levels ALARP by the Sponsor, and are described as follows:

Airflow Interruption: In rare cases, blockage of the bore of the investigational 3.0T Neonatal MRI device, particularly at the head end of the scanner, can cause interruption of normal airflow in the bore of the scanner. Through proper measurement of the subject, combined with visual inspection of the bore of the scanner once the subject is placed in the scanner, the scan operator will ensure that no blockage of the bore of the MR scanner exists.

Swaddler risk: Compression by the swaddle can cause discomfort and, in rare cases, more serious injury usually due to study procedures not being followed.

Fall: During transport or scanning, infants and neonates may be at increased risk of fall from the height of the MRI table or transport devices, typically due to improper use. The risk of fall is not expected to be greater than in routine transport and the height of all device components complies with regulatory requirements.

Like routine MRI scanning of <4.0T MRI, procedures conducted with the 3.0T Neonatal MRI investigational device rarely cause harm when performed as directed by trained staff using appropriate procedures, as described in this protocol, device documentation, and in Sponsor-provided training. The risks of AEs and SAEs have been mitigated by the Sponsor to levels ALARP. If the Sponsor learns any new information that would increase risk to subjects in this study, the PI will be notified in writing.

11.2. 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-patient 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 EC/IRB approved informed consent, protocol, investigator brochure, or product labelling.

Unanticipated adverse Device effect: 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.

11.3. Management of Adverse Event Reporting

Any adverse events will be recorded in the subjects study record and the Adverse Event Case Report Form. 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 aetiology 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 aetiology 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 that occur during a subject's active enrolment (as described in Section 6.3.1. - Pre-MR Scanning Activities: Duration of Active Enrolment) will be reported to the local EC/IRB per their policy and, if applicable, to regulatory agencies. Medical events that occur outside of

the active study during observational data collection, such as during standard of care follow-up conducted for any unexpected findings, will not be considered study adverse events.

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

All SAEs and or UADEs will be documented as above and reported 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 (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 and, if applicable, to regulatory authorities in accordance with their requirements.

Sponsor contact for SAEs and/or UADEs

Jeff Hersh, MD
+1-262-366-7295
Fax 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 Clinical Affairs

The Investigator shall submit the follow-up SAE and/or UADE report to the local/IRB per their policy.

11.5. Management of Device Complaints

Any complaints regarding the operation of the device or software or any malfunctions are to be reported to the Clinical Affair Project Manager

Sponsor contact for Device complaints:

Yvonne Celestial, Clinical Affairs Project Manager
Phone +33 130709133
Email MarieYvonne.CELESTIAL@ge.com

12. EARLY TERMINATION OR SUSPENSION

12.1. 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 the Sponsor determines to be appropriate

The Phase 1 Interim Report will be used by the Sponsor to determine if Phase 2 should be conducted and which version(s) of the *MR Procedure Document* will be applied in Phase 2. Consistent MR procedures will be used for all subjects throughout Phase 2.

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.

In the event of early termination after Phase 1, the Investigator remains responsible for completing a descriptive report of the results

12.2. Withdrawal of EC 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.

13. ETHICS COMMITTEE (EC) AND REGULATORY FILINGS

13.1. Regulatory Authority Approval Requirements (Global)

In the United Kingdom (UK) the use of the device is subject to regulation by the Medicines and Healthcare Products Regulatory Agency (MHRA), in compliance with the European Medical Device Directive 93/42/EEC. MHRA authorization is required prior to enrolling subjects. The Sponsor will notify the PI in writing to authorize subject enrolment.

13.2. Ethics Committee Approval Requirements

This study is to be submitted to the EC/IRB 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.

13.3. Management of Protocol Revisions/Amendments

All protocol amendments will be approved and released by the Sponsor.

13.4. Informed Consent and Privacy Requirements

Per European Medical Device Directive 93/42/EEC, the following will be required for all neonate/infant subjects enrolled in this study:

a. The parent(s), or guardian(s), or legally authorized representative(s) will be required to sign the informed consent form;

b. If it is the determination of the EC/IRB that both parent(s) or guardian(s) sign the informed consent form, that will occur except in the case of deceased, unknown, incompetent, or not reasonably available parties, or when only one parent has legal responsibility for the care and custody of the child if consistent with (EU) law and any other applicable laws and/or regulations at the site where the study is being conducted.

c. Permission by parents or legally authorized representative will be documented in accordance with, and to the extent required, by ISO 14155: 2011 (EU).

Informed consent will be documented in each subject file.

The Investigator or designee will consent the subject's parent(s), or guardian(s), or legally authorized representative(s) per regulatory guidelines, which includes the right to have ample time to review the ICF and have all questions answered to their satisfaction. Subjects may sign the ICF at the time it is presented if all of his/her questions have been answered. In the event that a the parent(s), or guardian(s), or legally authorized representative(s) require additional time or wishes to discuss the ICF with others, he/she will be allowed to take the ICF home prior to signing to review with family members or others before making a decision.

The parent(s), or guardian(s), or legally authorized representative(s); the person who consented the subject; and the investigator must sign and date the ICF document prior to a subject being included in the study.

The subject's parent(s), or guardian(s), or legally authorized representative(s) will be given a copy of the signed informed consent form and the original will be retained with subject files.

13.4.1. Consent for International Transfer and Use of Deidentified Data

The informed consent form (ICF) will explain that some data collected as part of this study may be transferred outside of the European Union (EU), including to the United States (US) and to other countries which may not provide the same level of data protections as the EU. Steps will be taken in order to protect the confidentiality of the data subjects. Applicable local laws and regulations for the transfer and use of clinical study data will be followed.

14. DATA AND QUALITY MANAGEMENT

14.1. Management of Data

Images and data will be collected from subjects enrolled in this study and pseudonymised using subject identification designation (SID). The resulting data will be key-coded and will not contain any direct identifiable personal information (e.g. no name).

GE Healthcare and authorized representatives may use image and associated data from this study for future technology development, marketing purposes, publications, regulatory use or

any other possible use. The images and associated image data collected from unexpected findings may be used for engineering development and device optimization purposes. Phase 2 data is collected with the intent of use in regulatory submissions, such as CE mark.

The approved Data Management Plan (DMP) will be located in the study's clinical history file maintained by the Sponsor.

14.1.1. International Transfer and Use of De-identified Data

In the case where personal data is transferred outside of the European Union (EU), it will be transferred to the United States (US) and other countries which may not provide the same level of data protections as the EU. Steps will be taken in order to protect the confidentiality of the data subjects. Applicable local laws and regulations for the transfer and use of clinical study data will be followed.

14.2. Subject De-identification

Not Applicable This section is not applicable for studies conducted in this region and is superseded by Section 13.3 Subject Pseudonymisation.

14.3. Subject Pseudonymisation

All subject data that is submitted to the Sponsor will be identified by the use of a unique subject number assigned as an identification code to the Subject, without de-identification. The scan operator will enter the identification number in the system to complete pseudonymisation.

The assigned subject identification number according to the Sponsor's Data Management Plan (DMP).

Each participating site will maintain a subject identification log, which is a list of all subjects who are enrolled in the study, along with their address and medical record number in the event that they must be contacted in the future.

The Sponsor will not receive a copy of the subject identification log

14.4. Completion of Case Report Forms (CRFs)

Data will be collected using paper CRFs, and data file transfers.

GEHC will provide CRFs and the instructions for their completion.

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 CRF for each subject who is enrolled to participate in this study. CRFs will be completed as information becomes available.

If errors or omissions are found in the course of a CRF audit, or data review, a *Note to File (NTF) or Data Clarification Form (DCF)* will be generated and the error, omissions or clarifications will be corrected on these forms.

The Principal Investigator will sign and date the indicated places on the CRF.

The Principal Investigator's signature will indicate that a thorough inspection of the data has been made and will thereby certify the contents of the form.

14.5. Record Retention at the Site

All records pertaining to the conduct of the study, including Case Report Forms, 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. These records will be maintained according to GEHC Retention Policies. Elements should include the following:

- Subject Files – containing the completed subject CRFs
- Regulatory Binder – containing the protocol and amendments, EC/IRB submissions and approvals, (blank and signed/dated) Informed Consent Form(s), and Site study logs
- 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 central supplier instructions.

No records will be destroyed without GE Healthcare notification and approval.

15. MONITORING PLAN

15.1. 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, EC/IRB review of the study, maintenance of records, primary outcomes review and review of the CRFs and source documentation for accuracy and completeness.

15.2. Reference to Approved Monitoring Plan

The approved monitoring plan will be located in the study's clinical history file (CHF) maintained by the Sponsor.

16. PUBLICATION POLICY

The Sponsor and its authorized representative may also utilize the images and data, in a fully anonymized format, for scientific publication(s), presentation(s) at scientific meetings or trade shows, product development, marketing materials, educational and training, support of global regulatory submissions, or other purposes authorized by the Sponsor in accordance with applicable laws and regulations.

Publications by investigators, study staff, and others involved with the study and/or investigational site will be governed by the contractual agreement between the Sponsor and site.

17. ADDITIONAL COUNTRY-SPECIFIC REGULATORY REQUIREMENTS

Applicable regulations in the UK will be followed in this study.

17. REFERENCES

1. US FDA *Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical D* May 14, 2004.
2. Malik S, Beqiri A, Price A, Teixeira J, Hand J, Hajnal J. Specific absorption rate in neonates undergoing magnetic resonance procedures at 1.5 T and 3 T. *NMR Biomed* 2015;28(3):344-52.
3. Glass H, Bonifacio S, Sullivan J, et al. MRI and Ultrasound Injury in Preterm Infants with Seizures. *J Child Neurol* 2009;24(9):1105-1111.
4. Arthur R. Magnetic Resonance Imaging in Preterm Infants. *Pediatr Radiol* 1:593–607.
5. Barkovich A. R Imaging of the Neonatal Brain. Neuroimaging Clin. N. Am. 2006;16:117–35– viii–ix. *Neuroimaging Clin N Am 2006* 2006;16:117–35– viii–ix.
6. Arthurs O, Edwards A, Austin T, Graves M, Lomas D. The challenges of neonatal magnetic resonance imaging. *Pediatr Radiol* 2012;42(10):1183-94.
7. Oishi K, Faria A, Mori S. Advanced Neonatal Neuro MRI. *Magn Reson Imaging Clin N Am* 2012;20:81–91.
8. Rutherford M, Biarge M, Allsop R. MRI of perinatal brain injury. *Pedatr Radiol* 2010;40:819–833.
9. Tkach J, Hillman N, Jobe A, et al. An MRI system for imaging neonates in the NICU: initial feasibility study. *Pediatr Radiol* 2012;42(11):1347-56.
10. Ment LR BHBPea. Practice parameter: Neuroimaging of the neonate: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002;58:1726–1738.
11. Kilian A, Schaible T, Hofmann V. Congenital diaphragmatic hernia: Predictive value of MRI relative lung-tohead ration compared with MRI fetal lung volume and sonographic lung-to-head ratio. *AJR* 192:153–158.
12. Dumoulin C, Rohling K, Piel J, et al. Magnetic Resonance Imaging Compatible Neonate Incubator. *Concepts in Magnetic Resonance 2002;15:11128.* 2002;15:117–128.
13. Whitby E, Griffiths P, Lonneker-Lammers T, et al. Ultrafast Magnetic Resonance Imaging of the Neonate in a Magnetic Resonance-Compatible Incubator with a Built-in Coil. *Pediatrics* 2004;113:e150–2.
14. Blüml S, Friedlich P, Erberich S, Wood J, Seri I, Nelson M. MR Imaging of Newborns by Using an MR-Compatible Incubator with Integrated Radiofrequency Coils: Initial Experience. *Radiology* 2004;231(594–601).
15. Rutherford M. MRI of the neonatal brain. *Saunders, UK* 2001. Available at: http://www.mrineonatalbrain.com.
16. Tkach J, Hillman N, Jobe A, Loew W, Pratt R. An MRI system for imaging neonates in the NICU: initial feasibility study. *Pediatr Radiol* 2012;42(11):1347-56.
17. Barkovich A, Kjos B, Jackson D, Norman D. Normal Maturation of the Neonatal and Infant Brain: MR Imaging at 1.5 T. *Radiology 1988* 1988;166:173–180.
18. Johnson M, Pennock J, Bydder G, Dubowitz L, Thomas D, Young I. Serial MR Imaging in Neonatal Cerebral Injury. *Am J Neuroradiol* 1987;8:83-92.
19. McArdle C, Richardson C, Nicholas D, Mirfakhraee M, Hayden C, Amparo E. Developmental Features of the Neonatal Brain: MR Imaging Part I. Gray-White Matter Differentiation and Myelination. *Radiology 1987* 1987;162:223–229.

20. Dumoulin C, Rohling K, Piel J, et al. Magnetic Resonance Imaging Compatible Neonate Incubator. *oncepts in Magnetic Resonance* 2002;15:117-128.
21. Stokowski L. Ensuring safety for infants undergoing magnetic resonance imaging. *dv Neonatal Care* 2005;5(1):14-27.
22. Plaisier A, Raets M, van der Starre C, et al. Safety of routine early MRI in preterm infants. *Pediatr Radiol* 2012;42(10):1205-11.
23. Benavente-Fernández I, Lubián-López P, Zuazo-Ojeda M, Jiménez-Gómez G, Lechuga-Sancho A. Safety of magnetic resonance imaging in preterm infants. *Acta Paediatr* 2010;99(6):853-8.
24. Chaves A, Cava J, Simpson P, Hoffman G, Samyn M. Infant cardiac magnetic resonance im using oscillatory ventilation: safe and effective. *Pediatr Cardiol* 2013;34(5):1201-5.
25. Blüml S, Wisnowski J, Nelson M, Paquette L, Panigrahy A. Metabolic Maturation of White Matter Is Altered in Preterm Infants. *PLoS One* 2014;9(1):e85829.
26. Stokowski L. Ensuring Safety for Infants Undergoing Magnetic Resonance Imaging. *Medscape Multispecialty: Advances in Neonatial Care* 2005;5(1):14-27.
27. Schenck J. Safety of Strong, Static Magnetic Fields. *J Mag Res Img* 2000;12:2-19.
28. Alibadi F, Askary R. Effects of Tactile-Kinesthetic Stimulation on Low Birth Weight Neonates. *Iran J Pediatr* 2013;23(3):289-294.
29. Anbeek P, Vincken K, Groenendaal F, Koeman A, Viergever M, van der Grond J. Probabilistic bra tissue segmentation in neonatal magnetic resonance imaging. *Pediatr Res* 2008;63(2):158-63.
30. Maalouf E, Counsell S. Imaging the preterm infant: practical issues. *Rutherford MA, ed. MRI of th Neonatal Brain*. London, England: WB Saunders; 2002.
31. Groenendaal F, Leusink C, Nijenhuis M, Janssen M. Neonatal life support during magnetic resonance imaging. *J Med Engin Technol* 2002;26:71-74.
32. ECRI. *Hazard report: patient death illustrates the importance of hering to safety precautions in magnetic resonance environments*. 2004.
33. Shellock F. Magnetic resonance safety update 2002: implants and devices. *J Magn Reson Imaging* 2002;16:485-496.
34. Formica D, Silvestri S. Biological effects of exposure to magnetic resonance imaging: an overview. *BioMedical Engineering OnLine* 2004;3(11).
35. McJury M, Shellock F. Auditory noise associated with MR procedures: a review. *J Magn Reson Imaging* 2000;12:37-45.

APPENDIX A: EXAMPLE OF INVESTIGATOR SUMMARY DOCUMENT

This Investigator Summary will be completed by the PI or delegate within approximately three (3) days of the Sponsor Investigator meeting conducted on: _____ _____
Date (DD/Mmm/YYYY) Start Time – End Time

Summary Number: _____	Applicable *MR Procedure Document* Version: _____

Subject Numbers (*record subjects that completed these procedures*):

Comments on current workflow, usability, scanning per MR Procedure Document listed above (*attach additional pages, if necessary*)

Comments/Suggestions for future Workflow, Usability, Scanning and/or Optimization (*attach additional pages, if necessary*)

_____ _____
Signature of Principal Investigator or delegate Date Completed

_____
Printed Name of Principal Investigator or delegate

_____ _____
Signature of Clinical Affairs Project Manager Date Received by Sponsor

_____
Printed Name of Sponsor Representative

Please submit the completed Investigator Summary within approximately 3 business days of each completing the activities described in the current MR *Procedure Document* Submit to:

Yvonne Celestial, Clinical Affairs Project Manager, *Phone* +33 130709133
Email: MarieYvonne.CELESTIAL@ge.com

APPENDIX B: EXAMPLE OF MR PROCEDURE DOCUMENT

The Sponsor provided this MR Procedure document on _____
Date (DD/Mmm/YYYY)

MR Procedure Document Version: ____ Effective date (begin study procedures on or after): _____
Date (DD/Mmm/YYYY)

Specific Instructions for procedures to be performed *(attach additional pages, if necessary)*

Sample Document – Not for Study Use
(Please use most current Sponsor-provided document version)

Sponsor-Requested Assessments of performance on a 5-Likert Scale *(mark each assessment required)*

☒ Overall Image Quality **(required for all subjects)**	**Other Assessments:**
Other Engineering Performance Measures	☐ _____ (specify)
☐ Performance parameter _____ *(specify)*	☐ _____ (specify)
☐ Performance parameter _____ *(specify)*	☐ _____ (specify)
☐ Performance parameter _____ *(specify)*	☐ _____ (specify)
☐ Image contrast	☐ _____ (specify)
☐ Artefacts	☐ _____ (specify)
☐ Fat/water homogeneity	☐ _____ (specify)
☐ Signal-to-noise ratio	☐ _____ (specify)
☐ Reconstruction software performance	☐ _____ (specify)
☐ Signal-to-noise ratio	☐ _____ (specify)
☐ Reconstruction software performance	☐ _____ (specify)

_____

Signature of Sponsor Engineering Representative Date

_____

Printed Name of Sponsor Engineering Representative

_____

Signature of Clinical Affairs Project Manager Date

_____

Printed Name of Clinical Affairs Project Manager

_____

Signature of Principal Investigator or delegate Date Received

_____

Printed Name of Principal Investigator or delegate

APPENDIX C – EXAMPLE OF INVESTIGATIONAL SINGLE USE DISPOSABLE SWADDLE LOG

Date of check-out	Swaddle Number	Check-out Time	Subject Number	Print name of Study Staff checking out swaddle	Study Staff Signature	Date of disposal of swaddle
Example: *17/Jun/2013*	*000*	*08:42 PM*	*000*	*Jane Smith*		*17/Jun/13*

APPENDIX D – EXAMPLE OF POSSIBLE SOFTWARE COMPONENTS

The software components listed below are an example of what may be used in subject scanning under an approved *MR Procedure Document* per the device configuration management and study protocol.

3-Plane Pulse Sequence Family	Spectroscopy PSD Family
FGRE	PROBE-P PRESS CSI single voxel
FIESTA	PROBE SVQ (PRESS and STEAM)
SSFSE	**Gradient Recalled Echo (GRE) Pulse Sequence Family**
SE Pulse Sequence Family	2D FIESTA
Spin Echo	2D Fat SAT FIESTA
IR	3D FIESTA
Echo Planar Imaging (EPI) Pulse Sequence Family	3D FIESTA with fat SAT
DW EPI including Focus	3D FIESTA-C
DW EPI Tensor	Fast GRE/SPGR (2D and 3D)
GRE EPI	2D GRE/SPGR (2D and 3D)
SE EPI	FGRE Time Course
One-click applications	2D FGRE with IR Prep (2D MDE)
3DASL	LAVA
BRAVO	2D MERGE
CineIR	SWAN
Silenz	ASSET Calibration
	Fast B1map
Fast Spin Echo Pulse Sequence Family	**Vascular Pulse Sequence Family**
FRFSE-XL	2D Fast Phase Contrast
FSE IR	2D Phase Contrast with Cine Mode
FSE-XL	3D Phase Contrast
FSE-XL Double/Triple IR	2D TOF-FGRE/SPGR
SSFSE	2D Fast TOF-FGRE/SPGR
	3D TOF-FGRE/SPGR
T1 FLAIR	3D Fast TOF-FGRE/SPGR
T2 FLAIR	fAstCINE
3D Cube	FastCINE PC
3D Cube FLAIR	Inhance 3D Velocity
3D FSE	
3D FRFSE-XL	

Visualization	Imaging Options
FuncTool DTI/FiberTrak	ARC
FuncTool DWI/eDWI	ART
FuncTool 3DASL	ASSET
FuncTool Fusion	Blood Suppression
FuncTool Spectro	Bright Blood (ASL)
FuncTool SER	Cardiac Gating/Triggering
FuncTool MR Standard	Classic
Volume Viewer: IVI	DE Prepared
Volume Viewer: Reformat	Extended Dynamic Range
Volume Viewer: 3D View	Flow Compensation
SAGE	Fluoro Trigger
SR Viewer	fMRI
Functool FMRI	IR Prepared
Viewer	Mag Transfer
Clariview	Multi-Phase
Add-Sub	No Phase Wrap
Flow Analysis	Phase Sensitive
Pasting	Real Time
	Sequential
	Tailored RF
	ZIP 512
	ZIP 1024
	ZIP x2
	ZIP x 4
	Grad Warp

APPENDIX E EXAMPLE OF MR SCAN LOG

The MR scan log will detail all scanning in this study and from other approved studies that use the same investigational MR device. Enter not applicable ("N/A") for fields that do not apply.

Scanner Generated Exam Number	Date of Scanning (DD/Mmm/YYYY)	GES/IIR study number (N/S for service, training, etc.)	Subject Number	MR Procedure Document Version (GES only, N/A for IIR/ service, training, etc.)	Anatomy Imaged (N/A for phantoms)	Comments

APPENDIX F – EXAMPLE 3.0T NEONATAL MRI INVESTIGATIONAL DEVICE USER EXPERIENCE QUESTIONNAIRE

This survey will be completed by an experienced scan operator once for each *MR Procedure Document* in Phase 1 and once at the end of Phase 2.

These survey questions will be completed by the scan operator for each patient on a scale of 1 to 5 or marked as 'not applicable' (N/A), as follows:

1 = strongly disagree
2 = disagree
3 = neither agree nor disagree
4 = agree
5 = strongly agree

Regarding your overall experience with the 3.0T Neonatal MRI investigational device, please rate each of the following on a 1-5 scale:

1. I think that I would like to use this system frequently
2. I found the system unnecessarily complex
3. I thought the system was easy to use
4. I think that I would need the support of a technical person to be able to use this system
5. I found the various functions in this system were well integrated
6. I thought there was too much inconsistency in this system
7. I would imagine that most people would learn to use this system very quickly
8. I found the system very cumbersome to use
9. I felt very confident using the system
10. I needed to learn a lot of things before I could get going with this system
11. I feel confident this system will meet my patient's needs
12. How likely is it that you would recommend this product to other professionals in your field?

This survey will be completed by an experienced scan operator once for each *MR Procedure Document* in Phase 1 and once at the end of Phase 2. Responses should consider the user's overall experience with the 3.0T Neonatal MR investigational device.

Questionnaire Instructions

Please take your time and carefully indicate your responses in the following scales below. PAY ATTENTION TO THE FACT THAT THE SCALES CHANGE their anchor points in the left and right columns from one question to the next. This is done in an effort to reduce bias in the results.

Based on your experiences interacting with the product how would you describe the product?

		Extremely	Somewhat	Slightly	Neither	Slightly	Somewhat	Extremely	
1)	Learnable	O---------	O---------	O---------	O---------	O---------	O---------	O	Not Learnable
2)	Inefficient	O---------	O---------	O---------	O---------	O---------	O---------	O	Efficient
3)	Resistant	O---------	O---------	O-------	--O---------	O---------	O---------	O	Responsive
4)	Annoying	O---------	O---------	O---------	O---------	O---------	O---------	O	Pleasing
5)	Satisfying	O---------	O---------	O---------	O---------	O---------	O---------	O	Dissatisfying
6)	Ineffective	O---------	O---------	O---------	O---------	O---------	O---------	O	Effective
7)	Fast	O---------	O---------	O---------	O---------	O---------	O---------	O	Slow
8)	Unfamiliar	O---------	O---------	O---------	O---------	O---------	O---------	O	Familiar
9)	Routine	O---------	O---------	O---------	O---------	O---------	O---------	O	Unusual
10)	Easy	O---------	O---------	O---------	O---------	O---------	O---------	O	Difficult
11)	Useful	O---------	O---------	O---------	O---------	O---------	O---------	O	Useless
12)	Bad	O---------	O---------	O---------	O---------	O---------	O---------	O	Good

APPENDIX G – EXAMPLE OF SINGLE-USE DISPOSABLE SWADDLE USER EXPERIENCE QUESTIONNAIRE

These assessments are designed to assess the usability the single-use disposable swaddle component associated with the 3.0T Neonatal MRI investigational device on a per patient basis. This survey will be completed by the scan operator for each patient that uses a swaddle.

These survey questions will be completed by the scan operator for each patient on a scale of 1 to 5 or marked as 'not applicable' (N/A), as follows:

1 = strongly disagree
2 = disagree
3 = neither agree nor disagree
4 = agree
5 = strongly agree

Regarding your overall experience with the Single-use Disposable Swaddle device, please rate each of the following on a 1-5 scale:

1. I think that I would like to use this swaddle frequently
2. I found the swaddle unnecessarily complex
3. I thought the swaddle was easy to use
4. I think that I would need the support of a technical person to be able to use this swaddle
5. I found the various functions in this swaddle were well integrated
6. I thought there was too much inconsistency in this swaddle
7. I would imagine that most people would learn to use this swaddle very quickly
8. I found the swaddle very cumbersome to use
9. I felt very confident using the swaddle
10. I needed to learn a lot of things before I could get going with the swaddle
11. I feel confident the swaddle will meet my patient's needs
12. How likely is it that you would recommend the swaddle to other professionals in your field?

GE Healthcare

Questionnaire Instructions

Please take your time and carefully indicate your responses in the following scales below. PAY ATTENTION TO THE FACT THAT THE SCALES CHANGE their anchor points in the left and right columns from one question to the next. This is done in an effort to reduce bias in the results.

Based on your experiences interacting with the product how would you describe the product?

	Extremely	Somewhat	Slightly	Neither	Slightly	Somewhat	Extremely	
1) Routine	O	O	O	O	O	O	O	Unusual
2) Inefficient	O	O	O	O	O	O	O	Efficient
3) Irrelevant	O	O	O	O	O	O	O	Relevant
4) Annoying	O	O	O	O	O	O	O	Pleasing
5) Satisfying	O	O	O	O	O	O	O	Dissatisfying
6) Ineffective	O	O	O	O	O	O	O	Effective
7) Fast	O	O	O	O	O	O	O	Slow
8) Unfamiliar	O	O	O	O	O	O	O	Familiar
9) Learnable	O	O	O	O	O	O	O	Not Learnable
10) Easy	O	O	O	O	O	O	O	Difficult
11) Useful	O	O	O	O	O	O	O	Useless
12) Bad	O	O	O	O	O	O	O	Good

APPENDIX H: AMENDMENT TO PROTOCOL VERSION 2.0

Purpose: This amendment document describes the changes from protocol version 1.0 to 2.0 to account for change in Sponsor medical monitor.

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	**Medical Monitor Name:**- ~~Roee Lazebnik~~ Jeff Hersh, MD **Address:** 3200 N Grandview Blvd Waukesha, WI 53188~~1678~~ **Telephone:**+1-262-366-7295~~262-312-1407~~ **E-mail:** ~~Roee.Lazebnik@ge.com~~ Jeff.Hersh@ge.com	Updated amendment version to reflect change in Sponsor medical monitor.
2	Section 10.4. Management of Serious Adverse Event and Unanticipated Adverse Device Effect Reporting	**Sponsor contact for SAEs and/or UADEs** ~~Roee Lazebnik~~ Jeff Hersh, MD +1-~~262-422-5126~~ 262-366-7295 *Fax* 800-888-3983 *E-mail*: SAE@ge.com	Updated amendment version to reflect change in Sponsor medical monitor.

APPENDIX I: AMENDMENT TO PROTOCOL VERSION 2.0

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

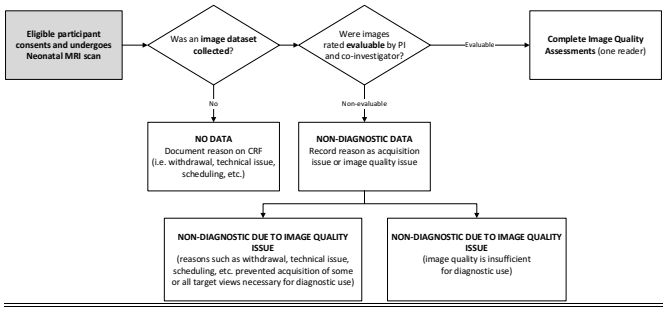
1. To clarify that the primary endpoint of the study is in accordance with Section 2.1 of Annex X of the EU Medical Devices Directive, which species that verification of performance across the study cohort is an essential requirement of the study.
2. To clarify that the planned duration of the study is 24-months, in accordance with requirements of ISO14155.
3. To add the feed and sleep procedure, as required by the local site IRB in accordance with the site standard of care requirements.

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
3	STUDY SYNOPSIS	This is a two~~-~~phase prospective clinical study evaluating the performance and safety of the investigational MRI device for neonates and infants including: …. Images, associated image data, and subject data collected in both phases of this study may be used for future engineering development and activities that support MR product development including Sponsor-authorized scientific and marketing activities. ~~Images and associated data from Phase 2 are intended for use as samples for~~ Summary evaluation of safety and performance from Phase 1 and Phase 2 may be used in support of regulatory submission including filings for European CE mark. ~~No cohort based analyses are planned for any phase of this study~~. … **Duration**: The study plans to actively enrol patients for approximately 24 months.	Per MHRA requirements in Annex 1 Section 2.1 of EU Medical Device Directive, clarified that the primary objective of the study is analysis of performance and safety of the device. In accordance with ISO14155, the 24 month planned duration of the study is specified.
4	Section 2.1.2. 3.0T Neonatal MRI Investigational Device Components and Initial Configuration	System Service Tool/Phantoms (Simulations):	Corrected typographical error of omitted punctuation (“/” mark).
5	Section 3.1. Hypothesis	There is no statistical hypothesis being tested in this study. Descriptive statistics will be used to provide summary evaluation of performance and safety data.	Clarified that an evaluation summary using descriptive statistics is required for EU regulatory submission.
6	Section 3.2. Justification	This study is being done in two parts to optimize and collect data from a new MRI device for use in neonates and infants, the 3.0T Neonatal MRI investigational device. The first part of this study is being conducted to demonstrate the feasibility of attaining diagnostic quality images and data using the 3.0T Neonatal MRI	Clarified that an evaluation summary using descriptive statistics is required

Item	Section	Revision or Clarification	Justification
		investigational device in neonates and infants with various hardware and software configurations. The second part of this study is being conducted to collect images and associated data i neonates and infants from a fixed hardware and software configuration of the 3.0T Neonatal MRI investigational device in support of regulatory activities in the European Union (EU), including CE mark.Summary performance and safety evaluations from both parts of the study may be disclosed to regulatory agencies as part of this study.	for EU regulatory submission.
7	Section 3.3.1. Primary Objective(s):	To evaluate the safety and performance of the device by collectio of ~~collect~~ images and associated data using the 3.0T Neonatal M investigational device that demonstrates the feasibility of use in clinical neonate and infant populations.	Per MHRA requirements in Annex 1 Section 2.1 c EU Medical Device Directive, clarified that the primary objective of the study is analysis of performance and safety of the device.
8	Section 3.4.1. Primary endpoints	For both Phase 1 and Phase 2, primary endpoints will be recorded as: • Collection of MR images and associated data per quotas (Section 5.1.1 - Quotas by Anatomic Region) • Performance will be determined by proportion of images determined to be of evaluable or non-evaluable diagnostic quality • Safety will be determine by summary rates of adverse events	Clarified the primary endpoint performance and safety measures, in accordance with revised objective described above.
9	Section 3.4.2. Secondary endpoints	• MR image quality evaluation(s), per-phase as follows: ○ *Phase 1 and 2 (all subjects): Overall ima quality rated on a 15 Likert scale* ○ *Phase 1*- Qualitative evaluation and optimization (Summary Report) provided b PI, as per applicable *MR Procedure Document* ○ *Phase 2*- Evaluations as described in the *MR Procedure Document*	Clarified that engineering performance endpoints are secondary. Per EU Annex X requirements, a measure of overall quality is required for all subjects in the study. The appendix is revised to clarify that this measure is required for all subjects in Phase 1 and Phase 2.
10	Section 4.1.1. Study Typ	This is a two-phase, single-site, open-label, prospective research study involving human neonate and infant subjects. ~~There will be no comparative or cohort-based statistical analyses of efficacy or safety, and therefore no randomization.~~ This study is designed as two-phase clinical trial with an adaptive feasibility and	Clarified that an evaluation summary using descriptive statistics is required

Item	Section	Revision or Clarification	Justification
		optimization phase (Phase 1) and controlled image collection stu (Phase 2). Phase 1 is being conducted to optimize and calibrate the device subsequent data collection in Phase 2 of this study. Both parts; ~~which is being done for~~ may be used for regulatory submission purposes, including CE mark and submissions to other global regulatory authorities in other countries. Not randomized: ☒ *Randomization is not required, as there ~~are~~ is no comparative ~~analyses~~ hypothesis testing*	for EU regulatory submission.
11	Section 4.1.2. Rationale for Two-Phase Study Design	Phase 2 Phase 1 will be followed by a sequential second phase (Phase 2) to collect human images and data intended to as sam images and associated per-subject data for use in regulatory submissions. ~~No comparative or cohort based analyses will be conducted on this population as part of this stud~~y.	Clarified that an evaluation summary using descriptive statistics is required for EU regulatory submission.
12	Section 5.8 Duration of Enrolment	**5.8 Duration of Enrolment** The study plans to actively enrol patients for approximately 24 months.	In accordance with ISO14155, the 24 month planned duration of the study is specified.
13	Section 6.2. Phase 1 (Adaptive Feasibility) an Phase 2 (Data Collectio	Phase2 will be conducted to collect sample images and associated data for regulatory submission. ~~No cohort based analysis is intended for this population, and data will only~~ be ~~recorded and stored on a per-subject basis.~~ While hardware and software may be modified throughout Phase 1, a fixed hardware and software configuration will be used for all Phase 2 scanning. Based on the results of Phase 1, *MR Procedure Document(s)* will be provided to the site and used consistently in all Phase 2 scanning.	Clarified that an evaluation summary using descriptive statistics is required for EU regulatory submission.
14	Section 6.3.1. Pre-MR Scanning Activities	**~~Pre-~~Study Feed and Sleep Procedures** Per the applicable standard of care procedures required at the investigational site, each participating neonate or infant subject will be allowed adequate feed and sleep to ensure minimum disruption of care during MRI scanning, as follows: c. The subject will be either breast or bottle fed by or in the presence of the parent/legal guardian. d. The subject will be placed in a position that is relaxed and comfortable, with the expectation that it will be reasonably possible for the subject to sleep through the MRI scan.	Added site IRB-required feed and sleep procedure, in accordance with local site standard of care requirements.
15	Section 6.3.4. Evaluations	**~~Image Assessments~~Evaluations** **~~Image~~ Performance Evaluation** Image sets will be ~~labeled~~ labelled according to subject identification number. Images will be evaluated as shown in Figure 2.	Added figure to clarify that evaluable/non-evaluable constitutes the primary performance measure. Added clarification that a third reader will

Item	Section	Revision or Clarification	Justification
		 **Figure 2**– Flowchart of performance evaluation. Determination of evaluable/non-evaluable for diagnostic used as the primary performance measure. All secondary Image Quality Assessments will be descriptively MR image datasets for each subject will be evaluated twice, once by the Principal Investigator and once by the neonatologist co-investigator or authorized designee as: • Evaluable (Diagnostic Quality), or • Non-evaluable (Non-Diagnostic quality). The printed name and signature of the image evaluator(s) will be recorded. In the event that the two readers disagree on whether an image is evaluable or non-evaluable, a third medically qualified reader will arbitrate to provide an evaluable/non-evaluable decision, which will be recorded to the CRF and treated as the final decision for the image set.	arbitrate to produce final evaluable/non-evaluable decision for inclusion in analyses, in the event of disagreement between the PI and neonatologist. This is required due to the addition of summary analysis of these data as required for submission for CE mark of the device in accordance with the EU Medical Device Directive.
16	Section 8.1.2. Statistical Analysis Methods	Images and associated data being collected in this study are intended for use on a per-subject basis. A summary evaluation of primary performance and safety endpoints and, if necessary, secondary image quality assessments will be prepared by the Sponsor and includes in the final clinical study report. Descriptive statistics may, as necessary, be used to summarize relevant results. This evaluation may be used for regulatory submission purposes. ~~No cohort-based analyses or descriptive summaries will be provided for any endpoint as part of this study.~~ Upon completion of this study, the Sponsor's authorized research and engineering program may utilize data collected in this study in full or in part for authorized engineering purposes.	Clarified that an evaluation summary using descriptive statistics is required for EU regulatory submission.
17	Section 9.0 OTHER INTERIM ACTIVITIES (QUALITATIVE INTERIM SUMMARIES)	**~~8.5.~~ 9.0 OTHER INTERIM ACTIVITIES (QUALITATIVE INTERIM SUMMARIES)** … **~~8.5.1.~~ 9.1 Phase 1 Qualitative Investigator Summary** … **~~8.5.2.~~ 9.2 Phase 1 and Phase 2 End-of-Phase Interim Reports**	Assigned separate numbering to this section to clearly indicate that these additional activities are not part of statistical analysis (Section 8 and its sub-sections). Correspondingly, attached sub-sections assume headings beginning with 9.X
18	Section 8.3. Handling of Missing Data	**~~8.4~~ 8.3 Handling of Missing Data**	Clarified that an evaluation summary

Item	Section	Revision or Clarification	Justification
		~~There are no cohort-based analyses.~~ The Sponsor may descriptively summarize the primary performance and safety endpoints from Phase 1 and Phase 2 of this study. If the Sponsor observed that the dataset for any subject is incomplete, additional clarification from the investigator may be requested. The Sponsor may additionally request copies of any clinical imaging datasets (including MRI scout datasets and other clinically indicated imaging examinations) that are conducted as follow-up to unexpected findings observed in this study.	using descriptive statistics is required for EU regulatory submission.The section is renumbered due to above explained separation of statistical and non-statistical and non-statistical sections into separate Sections 8 and 9, respectively, for clarity of original protocol intent.
18	Section 8~~4~~ Pass/Fail Criteria of the Study	**~~8.5~~ 8.4. Pass/Fail Criteria of the Study** The study will be considered successful if sufficient evidence is collected to inform the ~~evaluable sample images are collected from the~~ performance and safety of the 3.0T Neonatal MRI investigational device in a representative population of neonates and/or infants, in accordance with Annex X of the European Medical Device Regulation	Clarified that an evaluation summary using descriptive statistics is required for EU regulatory submission.The section is renumbered due to above explained separation of statistical and non-statistical and non-statistical sections into separate Sections 8 and 9, respectively, for clarity of original protocol intent.
19	APPENDIX ~~B~~EXAMPLE OF MR PROCEDURE DOCUMENT	☒ Overall Image Quality **(required for all subjects)** **Other Engineering Performance Measures** ~~**Performance**~~	Per EU Annex X requirements, a measure of overall quality is required for all subjects in the study. The appendix is revised to clarify that this measure is required for all subjects in Phase 1 and Phase 2.
20	Throughout	*Updated US English spelling conventions to conventional UK English spelling and MS word style throughout. No changes other than spelling were made throughout as part of this amendment, other than those documented in this appendix.*	Per UK best practice.
21	Throughout	*Removed the term "Adaptive" throughout.*	Per differences regarding implementation of

Item	Section	Revision or Clarification	Justification
			adaptive trialsin the EU, US, and other global regions, the term “adaptive” was determined to be misused in this context and could be misleading that the study is statistically adaptive (rather than adaption of iterative engineering parameters,as per protocol intent). This term is removed throughout to clarify the original protocol intent, and does not reflect a change in study design or risk level.

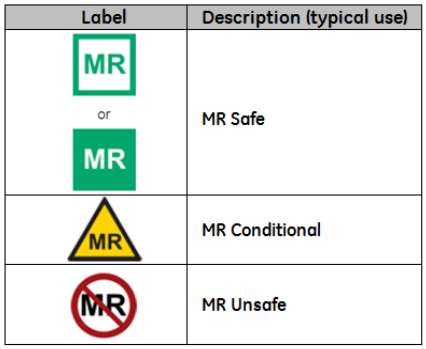
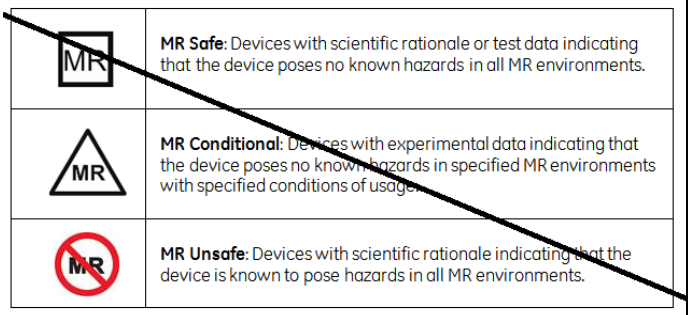
APPENDIX 1: AMENDMENT TO PROTOCOL VERSION 3.0

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

1. To clarify that MR system log files containing operating parameters relevant to device safety and performance models are being routinely collected for all study scanning.
2. To update references, symbols, and terminology, as requested for clarification purposes by the MHRA.

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.

Item	Section	Revision or Clarification	Justification
22	Investigator's Signature Page	I hereby agree to: (i) Conduct the investigation in accordance with the agreement, the investigational plan, applicable MHRA 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. ~~I have read this protocol and study related documents and agree to conduct this study in full accordance with the stipulations of the protocol described herein, and any subsequent amendments.~~	Updated required language for investigator signature pages, as per current Sponsor global template requirements. These changes are applicable for all clinical trials conducted by the Sponsor.
23	Synopsis: Device/Product Description	Small-footprint 3.0T Neonatal MRI investigational device capable of being located in a NICU and its components including a ~~neonate/infant~~ single-use disposable swaddle	Updated language for consistency with the terminology found in the body of the protocol.
24	Section 1.2. Literature Review	In particular, neonatal MRI has become standard clinical care for neurological and orthopaedic applications at many clinical facilities.[2,3,4,5]	Added citations to support this statement.
25	Section 1.4.1. Risks	While serious adverse events can occur in MRI exams in rare cases, typically with adverse events occurring as a result of ~~when~~ failure to correctly follow routine site MR safety procedures for scanning ~~are not correctly followed~~, no serious adverse events are anticipated in this study.	Clarified the language, as per original intent of the statement.
26	Section 2.1.1. 3.0T Neonatal MRI Investigational Device	This device includes an MR system	Correction to spelling (typographical)
27	Section 2.1.2. 3.0T Neonatal MRI Investigational Device Components and Initial Configuration:4.	The transmitting and receiving coil is a single channel ~~receive only~~ sixteen rung "birdcage" coil (inner surface accessible to the subject)	Clarified that the coil is for both transmit and receive functions.

Item	Section	Revision or Clarification	Justification
	Radiofrequency (RF) System		
28	Section 2.3Risk Category and Rationale	The MRI device used in this study uses static magnetic field strengths <4.0T, which are widely accepted to pose minimal risk to typical adults, children, and infants/neonate~~patients~~ as detailed in the US FDA Guidance *Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices* and contemporary medical literature~~, comparable with routine clinical MRI examination.~~[26, 27]	Clarified and added citation.
29	Section 2.3.1. MR Safe, Conditional, and Unsafe	 	Updated symbols to current version of ASTM F2503.
30	Section 2.5.5. Maintenance and Replacement: (a)	a. Access device(s) ~~in~~person or remotely (such as through TVA/Ti or other secure remote connection) for quality control, trouble shooting, training, real~~-~~time image optimization, to collect system configuration and system log files, or other purposes required for device maintenance, installation~~,~~ or de~~-~~installation, and/or system data collection;	Clarified that remote access is used as par of routine data collection of MR system log files.
31	Section 3.2. Justification	This study is being done in two parts to optimize and collect data from a new MRI device for use in neonates and infants, the 3.0T Neonatal MRI investigational device. The first part of this study is being conducted to demonstrate the feasibility and safety of attaining diagnostic quality images and data using the 3.0T Neonatal MRI investigational device in neonates and infants with various hardware and software configurations. The second part of this study is being conducted to collect images and associate data in neonates and infants from a fixed hardware and software	Clarified that operating parameters contained in system log files, such as SAR data, will be routinely collected as part of this study.

Item	Section	Revision or Clarification	Justification
		configuration of the 3.0T Neonatal MRI investigational device in support of regulatory activities in the European Union (EU), including CE mark.MR system log files containing operating parameters relative to safety and performance calculations will b systematically collected throughout the study for all subjects. Summary performance and safety evaluations from both parts of the study may be disclosed to regulatory agencies as	
32	Section 3.4.1. Primary endpoints	Safety will be determined by summary rates of adverse events	Correction to spelling (typographical)
33	Section 5.3.1. Vulnerabl Subjects	The Sponsor has conducted previous internal testing using phantoms to ~~confirm~~ evaluate the safety of the device for use on humans.	Updated terminology for consistency with internal Sponsor documentation.
34	Section 6.1.1. Quality Control Scans	The device is equipped with a predictive SAR model designed to conservatively limit actual SAR exposure in research subjects. T predictive SAR model used on the system is detailed in the technical documentation for the Neonatal MRI device. Each scan session will include sequences designed to generate a range of actual SAR data which is stored in ~~may be~~ system logs and subsequentlycollected by ~~the~~ Sponsor's engineering representatives ~~from system data and logs of study procedures~~ Throughout the study, system log files containing experimentally generated SAR data will be routinely collected, along with relevant clinical data such as patient weight (*as described in subsequent protocol sections*), necessary for future evaluation of the system's predictive SAR model versus actual clinical data in the infant/neonate population. ~~SAR levels will not exceed levels of 4 W/kg Whole Body, 3 W/kg~~	Clarified that MR system log files containing operating parameter data, including SAR data, will be routinely collected. This data is intended for use in evaluating engineering modelling of SAR in this population.
35	Section 6.3.2. MR Scanning Procedures: MR Scanning Information	Anatomy scanned (i.e. neurological (head/neck/spine) ~~cardiac/thorax, or abdominal/pelvis~~)	Corrected erroneous statement. All scanning in this protocol is of the neurological (head/neck/spine) anatomy. Other studies are being concurrently conducted by the Sponsor that examine additional anatomy types.
36	Section 11.1. Foreseeable Adverse Events and Device Effects	***Peripheral Nerve Stimulation:*** Transient skin sensations ('tingling' or peripheral nerve stimulation (PNS) is related to dB/dt and gradient rise time, and is expected to be rare in neonates and infants due to small skin surface area and conservative device thresholds.[26] Subjecting infants to sudden, rapidly changing gradient magnetic fields during imaging can, induce circulating currents in conductive tissues of the body that typically are not	Clarified PNS risk as per current medical literature, including citations.

Item	Section	Revision or Clarification	Justification
		painful and resolve~~Resolution is typically~~ spontaneously, though, in theory, discomfort or pain~~rare cases can cause discomfort or pain. injury~~ from PNS in infants is possible.[26] ~~or death.~~	
37	References	*2. Malik S, Beqiri A, Price A, Teixeira J, Hand J, Hajnal J. Specif absorption rate in neonates undergoing magnetic resonance procedures at 1.5 T and 3 T. NMR Biomed. 2015;28(3):3[illegible]4.* *3. Glass H, Bonifacio S, Sullivan J, et al. MRI and Ultrasound In Preterm Infants with Seizures. J Child Neurol. 2009;24(9):1103.* *27. Schenck J. Safety of Strong, Static Magnetic Fields. J Mag R Img. 2000;12:219.* *28. Alibadi F, Askary R. Effects of Tactile Kinesthetic Stimulation on Low Birth Weight Neonates. Iran J Pediatr. 2013;23(3):299.* *29. Anbeek P, Vincken K, Groenendaal F, Koeman A, van Osch M, va der Grond J. Probabilistic brain tissue segmentation in neonatal magnetic resonance imaging. Pediatr Res. 2008;63(2):158*	Added references to support the added citations in the document, and renumbered references appropriately in order of sequential appearance in the document.

APPENDIX K: AMENDMENT TO PROTOCOL VERSION 4.0

Purpose: This amendment document describes the changes from protocol version 4.0 to 5.0, as follows:

1. To clarify body temperature measurement and associated procedures for setup and calibration of the Invivo Expression monitor for monitoring of body temperature during MRI scanning.

The following amendments were made to version 4.0 to produce version 5.0. 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
38	Section 2.1.4. Other MR Equipment	Invivo Corp patient monitors will be used during study procedures to monitor subject vital signs body temperature (on the Expression Monitor using a single use sensor), and O_2 saturation.	Added text to clarify the original intent that body temperature is measured during scanning using the MRI compatible Expression Monitor.
39	Section 6.3.1. Pre-MR Scanning Activities	**~~Pre-scan~~ Transport Subject Information** The following prescan session subject information will be recorded for all subjects: • gender • age since birth (days for subjects aged ≤30 and months for subjects aged >30 days) • gestational age (for subjects ≤30 days old) • infant or neonate status (neonate = birth to ≤30 days; infant >30 days to <2 years) • *Pre-transport temperature* body temperature ~~measured~~ just before leaving the incubator or crib, measured according to the standard clinical practice at the investigational site as follows: ○ temperature measurement value ○ device type (Expression Monitor [Invivo] or standard of care device), and ○ anatomical area of measure (specific area of skin surface, i.e. axillary or specify; oesophageal; or other, specify)	Differentiated between pre-scanning and pre-transport procedures. Added specific requirements for capturing the value, device type, and anatomical area for temperature measures in the pre-transport period.
40	Section 6.3.1. Pre-MR Scanning Activities	**Preparation for Scanning** Immediately before initiating the scan, ensure that the Expression Monitor (Invivo) is connected and monitoring vital signs, including but not limited to body temperature and O_2 saturation. Once acclimated to the scan environment, the following scanning information shall be recorded by the scan operator, including the following: • *Pre-scanning baseline temperature* body temperature measurement made with an Expression Monitor (Invivo), as follows:	Added a new temperature measurement during the period in the MRI area immediately before scanning, This is collected as a baseline for confirmation that the subject's body temperature does not exceed 0.5°C during scanning. All temperature measures during scanning

Item	Section	Revision or Clarification	Justification
		○ the time (minutes) allowed for acclimation once in the magnet bore before taking the temperature measurement ○ temperature measurement value ○ anatomical area of measure (specific area of skin surface, i.e. axillary or specify; oesophageal; or other, specify). The study staff will set the alarm level on the Expression Monitor (Invivo) to trigger at 0.5°C above the pre-scanning baseline temperature.	will be taken using the Invivo Expression Monitor that is MRI compatible.
41	Section 6.3.2. MR Scanning Procedures	**Monitoring Subjects During MRI Scanning** During MRI scanning, subjects will be monitored in real-time using a properly functioning Expression MRI Patient Monitor (Invivo, Corp; Orlando, FL, USA). The subject will be observed all times during the MR scan by a qualified medical professional (nurse, neonatologist, and/or other medical doctor qualified for neonatal/infant care) on the study staff who shall remain in the magnet room with the subject during scanning. The observing staff should remain in a position where they can readily observe the subject and monitor and, if necessary, contact the scan operator during the scanning session. A conservative threshold for body temperature alarm is selected, as such that body temperature change is sufficient to trigger an alarm (0.5°C above the pre-scanning baseline temperature) is not in itself considered a clinically significant risk to patients; these patients will be evaluated by a medically qualified member of the study staff for any other possible signs or symptoms and they will determine whether an AE has occurred as per the standard procedures described in Section 11 – Complaint Handling and Adverse Event Reporting. If a body temperature alarm on the monitor is triggered at any time during scanning, the study staff should stop the scan series. Then, the following elements will be documented as part of study data for each such alarm occurrence: ○ the time of alarm ○ *Alarm Temperature* the body temperature at time of alarm, based on body temperature measurement made with an Expression Monitor (Invivo) as follows: ▪ temperature measurement value ▪ anatomical area of measure (specific area of skin surface, i.e. axillary or specify; oesophageal; or other, specify). ○ the time it takes to return to pre-scanning baseline temperature (minutes/seconds)	Describes that scanning will end if the temperature alarm indicates that body temperature rose more than 0.5°C during MRI scanning, and documents applicable temperatures and if the scan was able to be successfully continued upon resolution of temperature rise. Added that the actual body temperature at alarm and, if applicable, upon continuing the scan will be captured. It is clarified that the 60 minute scanning window only refers to the scanning time in the MR device, and not to setup or preparation time,

Item	Section	Revision or Clarification	Justification
		Note: In the event that the baby's body temperature does not return to a level at or below the pre-scanning baseline temperature within the study scanning period (not to exceed 60 minutes from first localizer to end of scanning), the patient will be discontinued from the study. ○ any conditions observed that possibly contributed to temperature rise, such as swaddling, environmental conditions, distress, or scanning conditions? (Y/N, if yes explain) ○ decision to continue the scan session (do not continue after first alarm)? (Y/N) ○ *Continuing Temperature*: the body temperature at the time of scanning was continued using an Invivo Expression Monitor, as follows: ▪ temperature measurement value ▪ anatomical area of measure (specific area of skin surface, i.e. axillary or specify; oesophageal; or other, specify). A medically qualified investigator should evaluate each patient to determine if it is safe to continue scanning once the patient's body temperature returns to pre-scanning baseline temperature or lower in the event of an alarm. If an alarm is triggered more than once during a single scan session, the patient will be discontinued. **Subject MR Scanning Procedures** The total time ~~that the subject may be in the MR scanner,~~ starting from the start of the first localizer to the time at the end of the last scan~~,~~ will not exceed sixty (60) minutes. Additional time may be required for setup and removal of the patient.	
42	Section 6.3.3. Post-scanning MR Procedures	**Post-scanning Subject Information** Post-scanning information will be recorded for all subjects: • *Post-scanning temperature*: Body temperature, immediately before removal from the MR scanner (post-scan body temperature), body temperature measurement made with an Invivo Expression Monitor and anatomical area of measure (specific area of skin surface, i.e. axillary or specify; oesophageal; or other, specify). • Time of removal from MR device (on 24 hour clock) • *Final temperature*: Body temperature ~~-~~ (measured after transport and just before the subject is ~~moved~~ placed ~~back~~ into ~~their~~ the routine care environment ~~incubator/crib by the same method used for previous body temperature recordings~~, as follows: ○ temperature measurement value	Differentiated between post-scanning and final temperature measurements. Added specific requirements for capturing the value, device type, and anatomical area for temperature measures in the post-transport period.

Item	Section	Revision or Clarification	Justification
		○ device type (Expression Monitor [Invivo] or standard of care device), and ○ anatomical area of measure (specific area of skin surface, i.e. axillary or specify; oesophageal; or other, specify) ***Note***: It is preferred that the same method as used for the *Pre-transport Temperature*)	
43	Section 8.3. Handling of Missing Data	The Sponsor may descriptively summarize the primary performance and safety endpoints from Phase 1 and Phase 2 of this study, including the descriptive statistical summary of patients that exhibit a body temperature rise of more than 0.5°C from acclimated pre-scanning baseline body temperature (resulting in an Expression Monitor alarm during scanning)	Describes intent to include the body temperature in descriptive statistic summary.
44	Signature Page		Updated to per current Sponsor procedural requirements.

APPENDIX L: AMENDMENT TO PROTOCOL VERSION 5.0

Purpose: This amendment document describes the changes from protocol version 5.0 to 6.0, as follows:

1. To clarify temperature measurement procedures, including that only the MR Safe Invivo Expression monitor may be used during MR scanning and in the MR scan room; standard of care methods may be used for temperature determinations in the patient's clinical care area.
2. Clarified that InVivo Essential monitor is not a required patient transport monitoring system and that site will use their standard of care monitoring system during patient transport. All mention of InVivo Essential monitor is removed from the protocol.
3. To clarify that if scanning is stopped due to alarm, the scanning will be discontinued, but patients may continue on in other parts of the study (i.e. transport) and that data from such subjects may still be used and disclosed to the Sponsor.

The following amendments were made to version 5.0 to produce version 6.0. 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
45	Section 2.1.4. Other MR Equipment	Invivo Corp patient monitor will be used during study procedures to monitor subject vital signs body temperature (on the Expression Monitor using a single-use sensor in the MRI scan room) and O2 saturation. ~~Essential Monitor (Invivo Corp) This is a patient transport monitoring system. This is MR Conditional patient monitor system labelled for use in neonate and infant populations that may remain in the magnet room during scanning if conditions are met. This is a small monitor that attaches to the patient table for transport purposes~~.	Clarification to when monitor may be used. Clarified that InVivo Essential Monitor will not be a required patient monitoring system during transport. Site will use their own monitoring system as per their standard of care.
46	Section 6.3.1. Pre-MR Scanning Activities	**General Method for Recording Temperature** Subject body temperature will be recorded at defined intervals before, during, and after scanning as detailed in the following sections. In the MR suite and during scanning, MR Safe Invivo Expression monitor should be used to determine temperature and other vital signs.	Clarification to when monitor may be used for study temperature measurements.

47	Section 6.3.1. Pre-MR Scanning Activities - Pre-Transport Subject Information	• *Pre-transport temperature* body temperature just before leaving the incubator or crib, measured according to the standard clinical practice at the investigational site, as follows:
		  ○ temperature measurement value
		  ○ device type (~~Expression monitor [Invivo] or~~ record standard of care device), and
		  ○ anatomical area of measure (specific area of skin surface ~~, i.e. axillary or specify; oesophageal; or other, specify~~)
			Clarified that Expression monitor is used during MR scanning.
			Corrected that standard of care temperature measurements will be used (Expression is only used in the MR suite.

48	Section 6.3.1. Pre-MR Scanning Activities - Pre-scan Environmental Condition	Immediately prior to the first scan series, the following environmental conditions in the MR scanning room will be recorded: • Scan room temperature • ~~System temperature, per MR device console~~	Clarified that the system console does not display this temperature and thus it cannot be recorded.

Item	Section	Revision or Clarification	Justification
49	Section 6.3.1. Pre-MR Scanning Activities – Preparation for Scanning	• *Pre-transport temperature* body temperature just before leaving the incubator or crib, measured according to the standard clinical practice at the investigational site, as follows: o temperature measurement value o device type (~~Expression monitor [Invivo] or~~ record standard of care device), and o anatomical area of measure (specific area of skin surface~~, i.e. axillary or specify; oesophageal; or other, specify~~)	Clarified that the site will not perform oesophageal measurements. Corrected that standard of care temperature measurements will be used (Expression is only used in the MR suite.
50	Section 6.3.1. Pre-MR Scanning Activities – Duration of Active Enrolment	Active enrolment will be considered to end on a per-subject basis upon the later of: a. The time that the subject is returned to his or her standard of care clinical environment ~~and~~ and all Sponsor provided devices are removed from the subject, including Sponsor-provided swaddle, protective padding, and all other study devices ~~OR~~ ~~b. The time that all Sponsor provided devices are removed from the subject, including Sponsor-provided swaddle, protective padding, and all other study devices~~. b. After active enrolment ends, images and data about any standard of care follow-up or other medical care resulting from unexpected findings may still be accessed observationally and collected by the Sponsor for research purposes.	Clarified end of subject active enrolment in the study.
51	Section 6.3.1. Pre-MR Scanning Activities – General Method for Recording Temperature	Subject body temperature will be recorded at defined intervals before, during, and after scanning as detailed in the following sections. In the MR suite and during scanning, MR Safe Invivo Expression monitors should be used to determine temperature and other vital signs. ~~Outside of the MR suite, Invivo Essential monitors should be used to determine temperature and other vital signs. In the event that these monitors are not able to be used for any reason, study temperature measurements may be taken using alternative standard of care body temperature measurement methods, and the type of body temperature measurement method should be documents on the CRF. Temperature and vital signs measurement devices used during scanning or in the MR suite must be labeled as MR Safe or meet the conditions of MR Conditional labelling.~~	Clarified and simplified the instruction of temperature collection. Clarified that in the MR suite, if for some reason InVivo Expression monitor is not working, the subject cannot be scanned at all. Outside of the MR suite, other devices can be used to monitor/measure the subject temperature.
52	Section 6.3.2. MR Scanning Procedures - Monitoring Subjects during MR Scanning	• *Pre-scanning baseline temperature* body temperature measurement made with Invivo Expression Monitor (Invivo), as follows: o the time (minutes) allowed for acclimation once in the magnet bore before taking the temperature measurement o temperature measurement value o anatomical area of measure (specific area of skin surface~~, i.e. axillary or specify; oesophageal; or other, specify~~).	Clarified that the site will not perform oesophageal measurements. Also clarified that scanning is discontinued in the event of alarm (subject is not necessarily withdrawn or

Item	Section	Revision or Clarification	Justification
		If a body temperature alarm on the monitor is triggered at any time during scanning, the study staff should stop the scan series. Then, the following elements will be documented as part of study data for each such alarm occurrence: ○ the time of alarm ○ *Alarm Temperature*: the body temperature at time of alarm, based on body temperature measurement made with the Expression Monitor (Invivo), as follows: ○ temperature measurement value ○ anatomical area of measure (specific area of skin surface; ~~i.e. axillary or specify; oesophageal; or other~~, ~~specify~~). ○ the time it takes to return to pre-scanning baseline temperature (minutes/seconds) ***Note***: In the event that the baby's body temperature does not return to a level at or below the pre-scanning baseline temperature within the study scanning period (not to exceed 60 minutes from first localizer to end of scanning), ~~the~~ patient ~~will be~~ scanning will be discontinued ~~from the study~~ (if collected, the patient's data collected up until this time may still be used for study purposes, and post-scanning information may still be recorded about the patient) ○ any conditions observed that possibly contributed to temperature rise, such as swaddling, environmental conditions, distress, or scanning conditions (Y/N, if yes explain) ○ decision to continue the scan session (do not continue after first alarm)? (Y/N) ○ *Continuing Temperature*: the body temperature at the time of scanning was continued using an Expression Monitor (Invivo), as follows: ▪ temperature measurement value ▪ anatomical area of measure (specific area of skin surface; ~~i.e. axillary or specify; oesophageal; or other~~, ~~specify~~). A medically qualified investigator should evaluate each patient to determine if it is safe to continue scanning once the patient's body temperature returns to pre-scanning baseline temperature or lower in the event of an alarm. If an alarm is triggered more than once during a single scan session, ~~the patient will be discontinued~~ scanning will be discontinued. If collected, the patient's data collected up until this time may still be used for study purposes, and post-scanning information may still be recorded about the patient.	discontinued from the study). Corrected that standard of care temperature measurements will be used (Expression is only used in the MR suite.
53	Section 6.3.3. Post-scanning MR Procedures - Post-scanning Subject Information	Post-scanning information will be recorded for all subjects: • *Post-scanning temperature*: Body temperature, immediately before removal from the MR scanner (post-scan body temperature), body temperature measurement made with and Expression Monitor (Invivo) and anatomical area of measure (specific area of skin	Clarified that the site will not perform oesophageal measurements. Clarified that Expression monitor is

Item	Section	Revision or Clarification	Justification
		surface~~, i.e. axillary or specify;oesophageal; or other~~, ~~specify~~). • ~~Time of removal from MR device (on 24 hour clock)~~ • *Final temperature* Body temperature measured after transport and just before the subject is placed into the routine care environment, as follows: ○ temperature measurement value ○ device type (~~Expression Monitor [Invivo] or~~ record standard of care device), and ○ anatomical area of measure (specific area of skin surface~~, i.e. axillary or specify; oesophageal; or other, specify~~) ***Note***: It is preferred that the same method as used for the *Pre-transport Temperature* • End of Enrolment Time: Time when the patient is returned to the clinical care area and all Sponsor-provided device components (i.e., Swaddle, Invivo monitor, pads, etc.) have been removed from the subject.	used during MR scanning, and Essential Monitor is used during transport (temperature measurements during transport are made according to the standard of care). Corrected that standard of care temperature measurements will be used (Expression is only used in the MR suite. Removed Time of removal from MR device (on 24 hour clock) and clarified end of enrolment time definition.
54	Section 6.3.3. Post-scanning MR Procedures - Post Scan Environmental Conditions	At the end of the last scan series when the scan operator enters the scan room to remove the subject from the MR device, the scan operator will record: • Scan room temperature • ~~System temperature, per MR device console~~	Clarified that the system console does not display this temperature and thus it cannot be recorded
55	Section 6.5 - Withdrawal and Discontinuation Criteria	All subjects must be admitted for care in the NICU or other neonatal or infant care department or unit affiliated with the investigational site at the time of enrolment and scanning to be eligible to participate in this study. If a subject is discharged from clinical care at the investigational site prior to MR scanning, the subject will be withdrawn from the study. The subject's medical care shall take precedence over any imaging or other procedures associated with the study. If it is determined during the exam that the study imaging will in any way negatively impact required clinical care, the subject shall be immediately withdrawn from the study. In the event the subject appears to be in pain or undue discomfort, if potentially destabilizing vital signs are observed by visual inspection or via monitoring equipment, or if the parent(s) or legally authorized representative requests to discontinue study procedures, the study procedures will be discontinued immediately and the subject will be removed from study~~-~~, as determined necessary by the medically qualified staff~~as soon as possible according to the standard of care~~ at the investigational site. The subject shall be removed from the MR environment as soon as safely possible, and, if necessary, care will be provided to the subject to alleviate any discomfort according to the site's standard of care. Data collected up until the time of withdrawal may still be used and disclosed to the Sponsor for research purpose	Clarified that data collected up until the time of withdrawal (even if scanning is discontinued) will be recorded.

Item	Section	Revision or Clarification	Justification
		The subject's parent or legal guardian may withdraw him or her from study participation at any time, for any reason without consequence. The study staff may withdraw a subject at any time for any reaso The reasons for withdrawal and discontinuation for any subject shall be recorded. These will be reported to the Sponsor.	
56	Section 14.3 Subject Pseudonymisation	All subject data that is submitted to the Sponsor will be identified by the use of a unique subject number assigned as an identification code to the Subject, without de-identification. The scan operator will enter the identification number in the system to complete pseudonymisation. The assigned subject identification number ~~will consist of a four digit number and be issued in consecutive order starting with 0001~~ according to the Sponsor's Data Management Plan (DMP). Each participating site will maintain a subject identification log, which is a list of all subjects who are enrolled in the study, along with their address and medical record number in the event that they must be contacted in the future.	Updated to reference this detailed description of numbering located in the DMP, as per standard Sponsor procedure.

APPENDIX M: AMENDMENT TO PROTOCOL VERSION 6.0

Purpose: This amendment document describes the changes from protocol version 6.0 to 7.0, as follows:

1. To clarify that the two (2) radiologists will act as image evaluators (rather than the PI and a neonatologist). This is done to minimize bias, as the PI and neonatologist may be directly involved in study acquisitions based on specific site practices.
2. Clarifies the responsibilities of evaluators and readers in this study in figures and flowcharts, for clarity only (this does not change the original intent or design of the study, other than as described in #1 above).
3. To clarify the roles of participating physicians and neonatologists in the study procedure and assessments.
4. To clarify the procedures for screenings subjects for enrolment and verify MR safety prior to study procedures.

The following amendments were made to version 6.0 to produce version 7.0. 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.

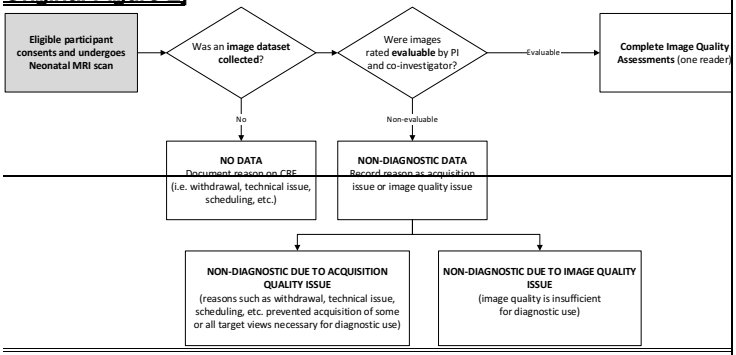
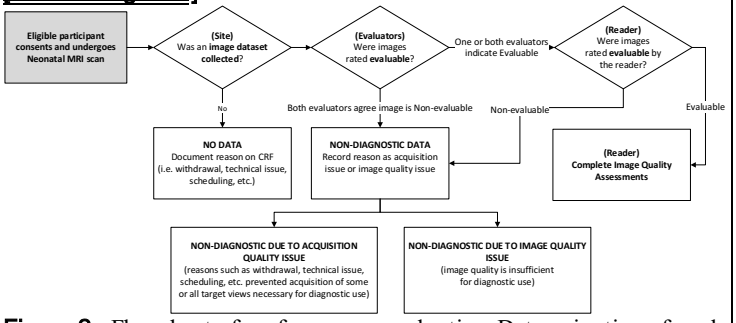
Item	Section	Revision or Clarification	Justification
57	Study Synopsis	**Duration**: The study plans to ~~actively~~ enrol patients for approximately 24 months.	Removed the descriptor “active” describing the EC/IRB approved protocol as this is not meant to correspond with the “active” enrolment period for AE reporting purposes. This term is removed to clarify this intent.
58	Section 2.6. Disposition of the Device/Product	When scanning under ~~all active~~ EC/IRB approved study protocols ~~is completed~~, the following actions will be conducted:	Removed the descriptor “active” describing the EC/IRB approved protocol as this is not meant to correspond with the “active” enrolment period for AE reporting purposes. This term is removed to clarify this intent.
60	Section 4.2. Controls and Minimization of Bias	The following bias control methods are being employed in this study: d. Selection bias will be limited by consecutively enrolling subjects meeting the inclusion/exclusion criteria e. Spectrum bias will be limited by using a population expected to be representative of the general population at the investigational site, without regard for gender, race, or ethnicity. f. Reader bias will be limited by ensuring that evaluators and readers making performance assessments are separate radiologists (not the PI or neonatologist).	Described added protections for reader bias by ensuring that the evaluators making image assessments are separate from the principal investigator.

Item	Section	Revision or Clarification	Justification
61	Section 5.4. Inclusion Criteria	4. Able to safely undergo an MRI scan, as determined ~~by the site's co-investigator neonatologist~~ medically qualified personnel 6. Are of appropriate size and shape to fit into the bore of th magnet, inclusive of all monitoring equipment, if any, necessary for the subject's routine clinical care based on standard of care measurement methods, in accordance with site policies	Clarified that the site would delegate medically qualified personnel, but this wil be done under the supervision of the PI and the Sponsor will not require that this be delegated to the site neonatologist.
62	Section 5.4. Exclusion Criteria	6. Have parent(s), guardian(s), or legally authorized representative(s) that require that they accompany the subject into the MR environment that have contraindications to the MR environment or would otherwise be put at undue risk or discomfort, as determined by ~~the investigators~~ medically qualified personnel;[8] 7. Have any ferrous or electrical items or non-removable medical devices that are not compatible with MR scanning (including devices labelled as MR Unsafe, MR conditional for which the scanning conditions are not met, or without MR safety labelling that does not satisfy site MR safety requirements) that may pose hazards in the MR scanning or MR environment, in the opinion of the Principal Investigator or medically qualified personnel ~~neonatologist co-investigator~~ in accordance with the site's MR Safety policy; 8. Have any contraindications or could otherwise be expected to experience detrimental effects to safety, well-being, or medical care, as determined by the Principal Investigator or medically qualified personnel ~~neonatologist co-investigator~~ in accordance with the site's MR Safety policy; 9. Require any scheduled standard of care procedures that are expected to be adversely impacted by participation in this study, in the opinion of the principal investigator ~~, neonatologist co-investigator,~~ or medically qualified ~~delegate~~ personnel; and	Clarified that the site would delegate medically qualified personnel, but this will be done under the supervision of the PI and the Sponsor will not require that this be delegated to the site neonatologist
63	Section 5.7 Screening and Enrolment	~~**5.7 Screening and Enrolment**~~ **5.6.2 Screening for Enrolment** Potential subjects will be identified by the Principal Investigator or other qualified site staff. Informed consent will be obtained for those subjects who agree to participate in the study. Subjects will then be screened for enrolment to ensure the subject is eligible to participate per the inclusion/exclusion criteria, as per the judgement of medically qualified personnel. Subjects who do not qualify based on inclusion/exclusion criteria will be considered screen failures.	Clarified screening requirements to specifically indicate that enrolment happens after consent is provided and before any study procedures are performed (including sizing ring).

[8] If it is not safe for the parent or guardian that wishes to accompany the subject into the MR environment, the parent or guardian may opt not to accompany the subject. In this case, the subject would not be excluded. Subjects would be excluded if it is determined to be potentially unsafe for a parent or guardian to accompany a subject into the MR scan suite, and the parent or guardian is not willing to allow the subject to be scanned alone while he/she waits in another area of the hospital.

Item	Section	Revision or Clarification	Justification
		Once a subject is determined to be eligible per the inclusion/exclusion criteria including providing written informed consent, the subject will be considered enrolled and assigned a subject number. ~~Subjects will be screened to ensure that all of the following conditions are met prior~~ to ~~study enrolment~~: ~~The subject meets the criteria for inclusion/exclusion, including size requirements~~, ~~*Note*: At screening, the subject's size will be determined according to the standard of care at the investigational site (e.g. using a tape measure other standard device). After informed consent is attained for~~ the ~~subject, the Sponsor provided sizing tool will be used to confirm the subject's size as part of MR safety screening~~. ~~Parents(s) or legal guardian(s) provide written informed consent for~~ the ~~subject's participation~~, ~~The subject and any person(s) accompanying him or her into the~~ MR ~~environment have been successfully screened according to the standard of care MR safety screening procedures at the investigational site~~(s), ~~including supplemental screening for patients that are suspected~~ to ~~have metal object on or implanted in their body (i.e. using hand held metal detectors), to ensure that both the subject and any person(s) who wish to accompany the subject into the MR scanning room are eligible for MR scanning. Written documentation will be retained by the site~~ for ~~MR safety screening~~. ~~If the subject and/or parent or other person that will accompany the subject fail to meet screening criteria, the subject will be considered as screen failure and will not be considered enrolled~~. ~~Subjects that meet the screening criteria will be enrolled and will~~ be ~~considered actively enrolled from the time the subject is placed on the swaddle, if used, or removed from his or her normal standard of care environment for transport until the subject is returned to his or her standard of care situation and all MR equipment, such as swaddle or padding, is removed~~. **~~5.7.1 MR Safety Screening~~** ~~Screening will be completed for the subject and any person accompanying him or her into the magnet room prior to allowing entrance into the MR scan room. The scan operator will confirm completion of MR safety screening, per standard clinical practice at the investigational site. In addition, subjects may be screened for the presence of ferrous metallic objects using a handheld metal detector, under the direction of the principal Investigator or delegate. The subject and anyone accompanying the subject into the MR scan room, will be provided with mandatory hearing protection, such as earplugs or ear plugs combined with earmuffs and/or ear plugs, and other protective devices required by site MR safety policies.~~ ~~Enrolled subjects must be confirmed to be of acceptable size for MR scanning in this study using the Sponsor provided sizing tool ("horseshoe" shaped ring) with all required attached medical equipment present This is conducted to verify that the subject and all necessary medical equipment can safely fit into the bore of the MR device with normal airflow and without contacting the bore., at the following intervals: Prior to removal from the normal clinical care environment Immediately prior to MRI scanning (by the scan operator or qualified designee)~~ ~~**Note**: The sizing tool is a study device that may only be used after written informed consent for participation has been attained~~.	

Item	Section	Revision or Clarification	Justification
64	Section 5.7. Duration of Enrolment	The study plans to ~~actively~~ enrol patients for approximately 24 months.	Removed the descriptor “active” describing the EC/IRB approved protocol as this is not meant to correspond with the “active” enrolment period for AE reporting purposes. This term is removed to clarify this intent.
65	Section 6.1.1. Quality Control Scans	The log will continue as long as the investigational MR device is housed at the site, and will only be discontinued when all ~~active~~ EC/IRB approved studies are completed and the investigational MR device(s) is/are removed from the investigational site. ***Note***: All human scans for this study, scans done for any other active EC/IRB approved ~~active~~ studies using this device, and other non-clinical scans (i.e. phantom scans for research, service/maintenance, or training) will be logged. This is done so that the log is consistent with the internal log inside of the system for engineering purposes. The log may contain other columns required by other concurrent protocols and some fields may be marked as not applicable (N/A) for other concurrent protocols.	Removed the descriptor “active” describing the EC/IRB approved protocol as this is not meant to correspond with the “active” enrolment period for AE reporting purposes. This term is removed to clarify this intent.
66	Section 6.3.1. Pre-MR Scanning Activities: MR Pre-screeening	**MR PreScreening** To verify that subjects with necessary medical equipment present can safely fit into the study device bore with normal airflow and without contact, subjects will be verified to be of acceptable size for study MR scanning using the Sponsor-provided sizing tool (“horseshoe” shaped ring) with necessary attached medical equipment prior to removal from the normal clinical care environment. **Note**: The sizing tool is a study device that may only be used after written informed consent for participation has been attained. The study staff will then ensure that the subject and any person(s) accompanying him or her into the MR environment satisfy all applicable site MR Safety Screening requirements. ~~The study staff will verify that enrolled subjects can be expected to safely undergo MR scanning according to the investigational site MR safety policy (which may include screening with handheld metal detectors, at the discretion of the PI). If the subject or any persons required to accompany him or her into the MR scan room are determined to be ineligible for MR scanning or if, for any reason, MR scanning would detrimentally impact any medical care that may be required or present undue discomfort to the subject or persons accompanying him or her into the scan room, the subject will be withdrawn from the study.~~ If the subject is determined not be of appropriate size, not to meet MR Safety Screening policies at the site, or is discharged from clinical care at the investigational site prior to MR scanning, the subject will be withdrawn from the study.	Clarified the difference between pre-screening that happens as a study procedure vs. screening for enrolment.
67	Section 6.3.1. Pre-MR Scanning Activities:Duration of Active Enrolment	**Duration of Active Enrolment (for AE/SAE reporting purposes)** Subjects may be transported to the MR suite before or after removal from their incubator, crib, or other standard of care bedding. Subjects will be considered active-enrolled (for AE/SAE reporting purposes) in the study on a per-subject basis from the time that the	Removed the descriptor “active” describing the EC/IRB approved protocol as this is not meant to

Item	Section	Revision or Clarification	Justification
		Sponsor-provided horseshoe-shaped sizing tool is used to measure subject size (the first study procedure of MR Pre-Screening). It is mandatory that the sizing ring is used for all subjects before other study procedures to ensure that the subject is of proper size for the MR bore.	correspond with the "active" enrolment period for AE reporting purposes. This term is removed to clarify this intent.
68	Section 6.3.1. Pre-MR Scanning Activities: Protective Devices/Procedures	All subjects require mandatory hearing protection that provides a minimum of 22 dB attenuation prior to MR scanning (ear plugs or a combination of ear plugs and ear muffs, in accordance with site MR Safety Polices). Use of the horseshoe-shaped sizing ring to verify that subjects can safely fit into the bore of the MR device is mandatory ~~and should also be performed before transporting the subject out of their clinical care environment~~ immediately prior to scanning. The scan operator or delegate will ensure that ~~A~~ the subject meets the criteria for MR scanning according to the ~~applicable site~~ specific MR safety site MR Safety Policy ~~procedures should be followed in addition to those specified in this protocol~~. In addition, the study staff may screen subjects and accompanying person(s) for presence of ferrous metallic objects using a hand-held metal detector, under the direction of the principal Investigator or delegate. If new information shows that the subject does not meet the site MR Safety Policy requirements, the subject will be withdrawn.	Clarified that ear plugs or a combination of ear plugs+muffs is required.
69	Section 6.3.4. Evaluations: Performance Evaluation	**Performance Evaluation** Image sets will be labelled according to subject identification number. Images will be evaluated as evaluable (diagnostic) or non-evaluable (non-diagnostic) by two evaluators, and then evaluable images will be read for image quality by a separate reader as shown in Figure 2. ~~Original Figure 2~~]  [Revised Figure 2]  **Figure 2**– Flowchart of performance evaluation. Determination of evalu the primary performance measure. All secondary Image Quality Assessn	Clarified text and Figure 2 to indicate that the PI will not be the study image evaluator, as an additional bias control.

<table>
<tr><th>Item</th><th>Section</th><th>Revision or Clarification</th><th>Justification</th></tr>
<tr><td></td><td></td><td>MR image datasets for each subject will be evaluated twice by two delegated radiologists serving as image evaluators (Evaluator 1 and Evaluator 2) ~~once by the Principal Investigator and once by the neonatologist co-investigator or authorized designee~~ as:
• Evaluable (Diagnostic Quality),[9] or
• Non-evaluable (Non-Diagnostic quality).
The evaluations and printed name and signature of the image evaluator(s) will be recorded to an Evaluator CRF. In the event that the two ~~readers~~ evaluators (Evaluator 1 and Evaluator 2) disagree on whether an image is evaluable or non-evaluable, a third medically qualified reader (Reader 1) will arbitrate to provide an evaluable/non-evaluable decision, which will be recorded to the Reader CRF and treated as the final decision for the image set.</td><td></td></tr>
<tr><td>70</td><td>Section 6.3.4. Evaluations: Image Quality Assessments</td><td>All evaluable images will be further examined by a single reader (Reader 1) that may be the PI or a qualified delegated radiologist for image quality on a 1-5 Likert Scale,[10] as follows:</td><td>Clarified reader roles.</td></tr>
<tr><td>71</td><td>Section 6.6. Study Flowchart (Table 3)</td><td>
<table>
<tr><th>…</th><th>Post-Scan</th><th>Reader/ Evaluator Assessments</th></tr>
<tr><td>Additional Sponsor-Requested Assessments</td><td>…</td><td>X (reader only) (defined in MR Procedure Doc)</td></tr>
<tr><td>MR Images and Data</td><td></td><td>X (access to)</td></tr>
<tr><td>Evaluable (Diagnostic)/Non-evaluable (Non-diagnostic) Assessment</td><td></td><td>X (reader and evaluators)</td></tr>
<tr><td>Image Quality Assessments</td><td></td><td>X (reader only)</td></tr>
<tr><td>Overall image quality (based on investigator's experience)</td><td></td><td>X (reader only)</td></tr>
</table>
</td><td>Clarified flowchart language around evaluators and readers. This is a clarification of the original intent, as described above.</td></tr>
</table>

[9] An image set may be considered of diagnostic quality if it contains images suitable for diagnosis (not all images views are typically required to be diagnostic based on specific scanning circumstances, so long as applicable views necessary for diagnosis are present)

[10] Likert Scale of 1-5, where:
1 = Very Poor
2 = Poor
3 = Neutral
4 = Good
5 = Excellent
Note: For image quality assessment, scores of 3, 4, or 5 will be considered diagnostic quality, and scores of 1 and 2 will be considered non-diagnostic quality.

Item	Section	Revision or Clarification	Justification
		Image contrast | | X (reader only) Presence of artefacts | | X (reader only) Signal to noise ratio (SNR) | | X (reader only) Tissue contrast | | X (reader only) Fat/water separation | | X (reader only)	
72	Section 11.1. Foreseeable Adverse Events and Device Effects	***Acoustic Noise:*** High noise levels in the scan room and in the bore of the scanner during MRI scanning may cause discomfort but are not normally hazardous with proper hearing protection. Spontaneously resolving hearing loss/tinnitus typically related to improper hearing protection can, in rare cases, become chronic or severe. Hearing protection (combination of earplugs ~~and/or~~ or ear plugs combined with earmuffs to achieve noise reduction of ≥22 dB is mandatory during MRI in	Clarified that ear plugs or a combination of ear plugs+muffs is required

End of Document