CLINICAL USE OF A NEW NEONATAL MRI SYSTEM

NCT01801865

April 6, 2017

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Date of initial submission to IRB: November 17, 2011
Version: April, 2017

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Study Location: Cincinnati Children's Hospital Medical Center (CCHMC)
Neonatal Intensive Care Unit (NICU)

ABSTRACT:

The current practice of transferring infants from the Neonatal Intensive Care Unit (NICU) to radiology departments and imaging in adult-sized magnetic resonance imaging (MRI) scanners is associated with significant safety and image quality issues. For these reasons, the smallest and/or sickest neonates are typically precluded from receiving an MRI exam. The overreaching goal of our research effort is to bring high-performance MRI into the NICU so that all neonates can benefit from the same quality of diagnostic imaging as adults. To accomplish this, we have converted a commercial small-bore 1.5 Tesla (T) MRI scanner designed for orthopedic use into a neonatal MRI system optimized for whole body imaging of neonates. To expand the imaging capabilities of the NICU MRI system, the measurement control electronics and operating system software of the FDA cleared imaging OPTIMA platform have been augmented with state of the art HDX electronics and software currently used on a conventional commercially available adult sized whole body MRI scanner. The clinical safety of the integrated HDX/OPTIMA NICU MRI system and its ability to produce diagnostic image quality has been shown in 15 pilot patients (CCHMC Protocol 2011-2045). The present protocol builds and expands upon the previous to use the integrated NICU MRI system to perform routine clinical MRI exams in the neonatal population. NICU patients for whom an MRI exam is medically indicated will be recruited for the present study. Routine clinical MRI exams will be performed using the FDA cleared OPTIMA NICU MRI platform and standard protocols. The exact MR imaging methods/procedures utilized will be determined by the type of exam (brain, lung, or abdomen) to be performed and the medical indication. Additional images will then be collected using the integrated HDX/OPTIMA NICU MRI platform using enhanced state of the art imaging techniques. All of the MR images obtained will be reviewed by a board certified pediatric radiologist and a standard report will be generated and included in the infant's medical record. The MRI data collected using the integrated MRI system will supplement those generated by the OPTIMA platform to inform diagnosis and guide subsequent medical management.

PURPOSE OF STUDY:

The purpose of the present study is to make medically indicated state of the art/high end MRI exams available to all infants who are CCHMC patients.

BACKGROUND:

Complications related to prematurity and congenital malformations are the most common cause of morbidity in infants, and now contribute almost equally to infant mortality[1-4]. The diagnosis and management of many of these medical conditions commonly seen in the NICU could be improved by MR imaging. While MRI has been widely available to the adult patient population since the early 1980s, its use for premature and term infants has been extremely limited. Although some studies have shown the potential of MRI in these patients [5-9], routine clinical use remains beyond reach due to the potentially life-threatening risks associated with moving a baby out of the NICU for the exam. Although transporting neonates between departments is possible and has been successful in a few institutions [5, 10-16], the diagnostic image quality of neonatal MRI suffers considerably

from the use of imaging technology optimized for adult anatomy[6-10, 17-29]. For example, when using an adult MRI receive coil array to image the chest of a 5 lb infant, most receive elements are too far away from the anatomy of interest to receive a clinically useful signal. This necessitates the use of increased imaging times to compensate for the poor signal-to-noise ratio which in turn leads to increased sensitivity to motion. Motion sensitivity is further exacerbated by the higher respiratory rates (30-60 breaths per minute) and heart rates (100-160 beats per minute) of neonates, and the fact that the infants are often not sedated for the MRI. To date, no extensive effort has been made to address these technological challenges in neonatal MRI.

In order to address the need for neonatal access to high-end diagnostic MRI instrumentation, engineers and scientists in the Imaging Research Center (IRC) at CCHMC have adapted a commercially available small (21.8 cm diameter bore, as compared to 60-70 cm for a conventional scanner) 1.5T MRI system, the GE OPTIMA 430s, originally designed for adult orthopedic use. The operating manual and data sheets for this MRI system are included as Appendix A. The OPTIMA measurement control electronics and operating system software have been augmented with HDX/GE electronics and software (see Appendix B: HDX/GE platform operating manual and data sheets). This integration of the HDX/GE electronics and the OPTIMA hardware allows for advanced MR imaging more relevant to whole body and brain scanning. The HDX/GE platform is FDA cleared and is used to operate much of the GE MRI product line. We have simply extended it to include their new magnet, the OPTIMA 430s. The original OPTIMA electronics will remain operational with the OPTIMA hardware with the option to readily switch between the two operating platforms (i.e. HDX/GE vs. OPTIMA).

An extensive detailed description of the modifications that were made to the systems to accommodate whole body MR imaging of the neonate and a detailed description of the patient table developed to accommodate the smaller size of the magnet are documented in the "BACKGROUND" section of CCHMC IRB Protocol 2011-2045 ("Pilot Study: Safety of a Customized MRI System for Neonatal Imaging") (See Appendix C: Detailed description of 1) modifications made to the MR systems to accommodate whole body MRI of the neonate; 2) patient table developed to accommodate the smaller size of the magnet).

PREVIOUS WORK IN THIS AREA:

Prototype MRI system installed in the BSL2 level laboratory in the CCHMC IRC:

Preterm sheep imaging experiments have been successfully completed on the modified OPTIMA MR platform and phantom and human imaging experiments have been performed on the integrated HDX/OPTIMA platform. Details about the methods and results of these studies are documented in the "PREVIOUS WORK IN THIS AREA" section of CCHMC IRB Protocol 2011-2045 ("Pilot Study: Safety of a Customized MRI System for Neonatal Imaging"). (See Appendix D. Previous work done in this area on prototype neonatal MRI system).

NICU MRI safety testing data:

Specific details about the MRI system's safety testing are documented in the Previous Work In This Area section of the protocol 2011-2045. The patient table, coils, SAR, acoustic noise, and peripheral nerve stimulation are all discussed. (See Appendix E: MR system safety testing data). We have completed 15 patients in the pilot study (CCHMC IRB Protocol 2011-2045). We observed 4 adverse events in these 15 patients -- 3 babies had oxygen saturation drops to the low 80s for about 5 seconds. One of these 3 babies also had a heart rate drop to the mid 80s for about 5 seconds. These were considered mild, not harmful to the patient, and not related to the MR scanner itself. Blowby oxygen was placed by the patient's head during the rest of the scan time and no further oxygen saturation drops were seen. The rest of the 15 patients tolerated the scanning process well. Image quality was for the most part excellent, although in some patients there was some motion artifact seen due to the lack of sedation given. Similar motion artifact is often seen in the currently available scanners when patients are not sedated. Images from one baby were directly compared to an MRI he had received the week before in Radiology (the intra-operative scanner) and were found to be of better quality. Photographs from the scanning process and images from the first patients are attached in Appendix F. Permission to use the photographs was obtained from the parents of the baby.

STUDY METHODS:

This is a study to use a customized MRI system installed in the CCHMC NICU to perform medically indicated MRI exams in the neonatal population.

Study population:

Neonates admitted to CCHMC for whom an MRI exam is medically indicated will be recruited into the study. All neonates in the study will be viable, as defined in subpart B of the Code of Federal Regulations. The infants will be medically stable to undergo the MRI procedure, as determined by the attending neonatologist.

Study design:

Infants who may meet study criteria will be identified by the attending neonatologist and study staff will be notified of a potential candidate for the study. As per usual clinical care, orders for the MRI will be placed in EPIC. Parents/Legally Authorized Representatives (LARs) will then be asked to sign a Parental Permission Form for the study. Some study participants may receive multiple neonatal MRI exams during their hospitalization/stay in the CCHMC NICU if the additional MR procedure(s) is(are) determined to be medically indicated by the attending neonatologist.

Inclusion criteria:

-Any infant admitted to CCHMC
-Have a medical condition for which an MRI exam is indicated, as determined by the attending neonatologist
-Parental/LAR permission obtained

Exclusion criteria:

-Infants too large to fit in the customized NICU MRI system comfortably (expected to be infants > 6 kg)
-Standard MRI exclusion criteria as set forth by the CCHMC Division of Radiology

Pre-scan:

The attending neonatologist will determine whether the MRI scan is to be done with sedation or without sedation. Whenever possible, infants will be scanned without sedation.

Infants will be prepared for the MRI exam at the bedside by switching all monitoring devices over to MRI compatible monitors. Switching monitoring devices confers no additional risk to the patient. Hearing protection will be used for acoustic noise reduction. Infants will then be moved to the MRI control room and transferred to the patient table/transfer station by the NICU nurse and/or physician.

MRI scan:

All studies will be performed with a nurse and/or physician in the control room.
The specific MR sequences used will be determined by the type of exam (brain, lung, or abdomen) to be performed based on the medical indication. Some patients may get IV contrast and/or sedation if indicated by the specific MR exam protocol. The scanner will be operated by a certified MR technologist.

Sequences will be obtained using the OPTIMA electronics during each MRI exam in order to have diagnostic quality images from a device that is FDA-cleared. Additional sequences will be obtained with the HDX/GE platform as part of the research study.

Coils used as part of this system may be standard coils purchased from GE or custom made coils that have gone through pre-clinical testing and operate within FDA approved limits. As new coils are developed their safety documentation and manuals will be submitted to the IRB.

Images from the HDX/GE platform are expected to be of diagnostic quality equal to or better than those obtained from an adult-sized 1.5T MRI scanner. Some study participants may receive multiple neonatal MRI exams (the type of each depending on the specific clinical condition to be evaluated) during their stay in the CCHMC NICU if the additional MR procedure(s) is(are) determined to be medically indicated by the attending neonatologist.

If the patient remains stable throughout the MRI exam, an additional 10 minutes of scanning beyond the clinically indicated sequences may be obtained for research purposes, similar to IRB protocol 2011-0572.

Monitoring of safety and tolerability:

Adverse events will be monitored during the MRI scan. Any adverse events that take place during the MRI procedure will be recorded on the adverse event log form. Also, the MR Safety Checklist will be included in the patient's research record (as per usual clinical care). Nurses will collect vital signs for clinical care purposes, but there will be no vital sign collection as part of this protocol.

Evaluation of MRI data:

As is done for any medically indicated clinical MRI exam, all images acquired will be read by a board certified pediatric radiologist or neuroradiologist and a standard report generated. This report will be included in the neonate's medical record and made available to the clinical team. The report will include language to indicate that some of the MRI data was collected using an Investigational Device. The MRI data collected using the OPTIMA/HDX MRI platform will be used in conjunction with the images obtained using the FDA cleared OPTIMA MRI platform and the results of other appropriate standard diagnostic tests to inform diagnosis and/or subsequent medical management. Deidentified images may be used in publications or in support of a 510K application to the FDA.

Collection of demographic data:

Each patient's weight from the night before the scan (obtained as per usual clinical care) will be recorded. Gestational age and postnatal age in days will also be recorded. This information will be used in order to facilitate future design of coils and transport tables for the customized MRI system.

Sample size:

The goal of this study is to make MRI available to all neonates admitted to CCHMC for whom an MRI exam is medically indicated. Thus, the maximum number of patients recruited into the study per year will reflect the maximum number of patients admitted into the NICU. A review of the historical data documenting the number of patients admitted to the CCHMC NICU over a five year period (2006 – 2010) indicated that on average, 714 (range 662-759) patients were admitted each year over that period.

DURATION:

This protocol is considered a continued access protocol and will remain open indefinitely.

POTENTIAL BENEFITS:

By eliminating the need to transfer neonates from the NICU to the main Radiology Department for an MRI exam, neonatal patients will benefit by avoiding the medical risk associated with removal from the NICU. Patients evaluated on the NICU MRI will also benefit from reduced acoustic noise, lower RF power deposition and less chance of peripheral nerve stimulation during the MR exam as compared to that associated with

exams performed on the adult sized MR scanner. Patients may also benefit from earlier and/or more comprehensive and accurate diagnosis and medical management.

POTENTIAL RISKS, DISCOMFORTS, AND INCONVENIENCES:

MRI exams are considered minimal risk for research purposes. The customized NICU MRI scanner will have no increase in risk beyond conventional adult MRI scanners. Although chart review is not part of this protocol, there is a risk of loss of confidentiality of medical record information. In order to protect the privacy of medical information, the research records will be coded and access to the records will be limited to research personnel. The MR report will be included in the clinical medical record to supplement diagnosis and medical management. All other study specific data (e.g. parental permission, safety record) will be de-identified and kept in a locked cabinet. No individual identifiers will be used in publications or reports resulting from the study. After the study is completed and the results are published, the records will be destroyed.

RISK/BENEFIT ANALYSIS:

In the opinion of the investigators, this study involves no increase over minimal risk with potential immediate and direct benefit to the study subjects and potential benefit to future patients and the scientific community. We believe that making MRI more readily available to this population will be of benefit to their subsequent medical management. In addition, infants in the study will in fact have less risk than they would during an MRI scan obtained on a conventional clinical MRI system as part of usual clinical care, due to the decreased risk of acoustic noise injury and the elimination of the risk associated with transporting the infant out of the NICU to the Radiology department.

SECURITY/CONFIDENTIALITY:

All subjects enrolled in this study will be identified by a unique study number only. The MR report will be included in the clinical medical record to supplement diagnosis and medical management. All other study specific data will be de-identified. Protected health information will be entered into a secure database. A single copy of a list linking medical record number to study number will be kept locked and available only to study investigators. All records will be kept in a locked cabinet at CCHMC and maintained by the study investigator. All computerized records will be password protected.

REIMBURSEMENT/PAYMENT FOR STUDIES:

The parents/LARs of the study patient and/or their medical insurance company will be responsible for the financial charges/costs associated with each of the MRI exams he/she receives using the OPTIMA NICU MRI platform while enrolled in the study. The costs associated with additional imaging performed using the OPTIMA/HDX NICU MRI platform will be assumed by the Department of Radiology. These costs will be identical to those incurred by patients who receive MRI exams on the adult sized conventional MRI scanners in the main Radiology Department. There will be no compensation or payment to the study participant.

RECRUITMENT:

Patients will be identified based on clinical need. After potential study subjects are identified, the study team or NICU attending physician will discuss the study with the parents/LAR and obtain parental permission.

Informational flyers or materials directed at healthcare providers and/or the general public may be created. All marketing materials will be approved by the IRB prior to circulation.

PLAN FOR OBTAINING PARENTAL PERMISSION:

All parents/LARs of prospective study patients will have the study explained by a member of the research team in language that is understandable to them. The nature of the tests and procedures to be done will also be explained along with the potential hazards, possible adverse reactions, and financial costs. It is understood that parents/LARs of infants in the NICU are often overwhelmed, and the study personnel who will consent the parents/LARs for this study will be familiar with how to obtain parental permission in stressful situations. It will be clearly stated that participation is voluntary and that refusal to participate will involve no penalty or loss of benefits to which their child is otherwise entitled. Informed parental permission will be obtained by the principal investigator, co-investigators, research personnel, or NICU attending physicians who are members of the research team. The research team will obtain parental permission from at least one parent/LAR and whenever possible, the study will be discussed with both parents/LARs. Non-English speaking participants will be consented using a short form consent process as per CCHMC SOP 41-1.8. The approved long parental permission form will serve as the summary of the research.

Informed parental permission will be obtained using Consent Management System. The Consent Management System (also known as eConsent Portal) was created by the Division of Biomedical Informatics at CCHMC (BMI) to allow researchers and electronic format to obtain and manage the consent records of participants within a secure database. It is currently in use for low-risk studies hosted by CCHMC's Research Foundation. The database will be accessible by research study staff for obtaining consent as well as those study members who will perform monitoring activities and administrative access by members of BMI. The database of the consent management application is encrypted to prevent unauthorized data disclosure. The connection between the application front-end and the database and between the application front-end and the user's web browser is also encrypted.

We intend to use the consent management in order to streamline our consent process. We will transition from paper consent to the electronic consent management system for all consents. If a LAR does not feel comfortable or competent using the electronic system, the medical fellows, who will receive training on the e-consent system, may help them navigate the system. When consent is obtained in-person, the medical fellow will sit with the legal guardian and explain and discuss the study with the legal guardian, as is done now under the currently approved protocol. However, instead of reading a hard-copy

consent, the legal guardian will be given time to read the consent on a computer or tablet. At the end of the consent, the LAR will be asked whether they have questions or concerns about anything they just read. Then, instead of signing a paper consent, the legal guardian will be guided through the e-consent system and be prompted to sign and date electronically.
After each consent is completed, the consent management system will notify the clinical research coordinator. The clinical research coordinator will then go into the consent management system and download the consent as a PDF and upload it into the patient's chart in EPIC. A copy of the consent will also be sent to the CCHMC HIM office.

The day of the scheduled MRI scan, the MRI technologist will access the patient's chart or the eConsent system in order to confirm that consent has been obtained before scanning begins. Only after the technologist has confirmed the consent is complete by viewing the PDF will the scan occur.

Prior to the initiation of the study, defined as initiating any procedure for purposes of evaluating patient eligibility not otherwise a part of routine patient care, acknowledgement of the receipt of this information and the parent's/LARs freely tendered offer to allow his/her child to participate will be obtained from the parents/LARs in the study.

In cases where parents/LARs are not physically present for the consent process, we are requesting a waiver of documentation of consent in accordance with 21CFR56.109. The research presents no more than minimal risk to participants and an MRI does not require written consent outside the research context.

In these cases we will use a phone consent process whereby a study staff member will discuss the research MRI with the parent/LAR. Documentation that consent for the study was obtained via verbal (phone) consent will be captured by designated study staff within the eConsent portal. When consent is obtained via phone, the medical fellow will fill out the e-consent themselves. They will also indicate on the informed consent process note that consent was obtained via phone. This process is identical to the already IRB approved process for obtaining consent via phone, with the exception of the medical fellow filling out the consent on the e-consent management system as opposed to on a paper consent form.
The system is run, monitored, and regularly tested for security by the CCHMC BMI department. This department works within secure institution technology guidelines and SOPs. The system will only be implemented on the CCHMC secure network. All of 21 CFR Part 11 does not apply to the electronic consent system we will be using because Part 11 is referencing electronic data management systems, which is not what we are using the electronic consent for. We are using the electronic consent system solely for consenting. Part 11 deals with electronic records, electronic signatures, and handwritten signatures in order to ensure they are trustworthy, reliable, and generally equivalent to handwritten signature executed on paper. In order to be considered equivalent to full handwritten signatures, the e-signatures must comply with all requirements under 21 CFR part 11. The system must capture and record the date that the subject's LAR provides

consent; which our electronic consent system does. Study team will not be sending consents to LARs. The fellow obtaining the electric consent will be in-clinic with the LAR who will have already been verified as the LAR.

This protocol, parental permission, and any amendments to the protocol will be reviewed by the CCHMC IRB prior to initiation. The study will not be initiated without the approval of the IRB. Written notice that the protocol and parental permission forms have been reviewed and approved by the IRB will be submitted to the investigator prior to study initiation.

Under very rare circumstances when obtaining consent via the eConsent Management system is not feasible, the IRB approved paper consent may be used. If a paper consent is used, it will be transitioned to storage in the eConsent management system.

DATA SAFETY AND MONITORING PLAN:

As the study involves no increase over minimal risk, no Data Safety Monitoring Board will be created for this study.

Source documents and case report forms will be completed for each subject. The case report form will serve as a source document for some items.

CONCURRENT RESEARCH PROTOCOLS:

Subjects will be allowed to participate in other research protocol(s) concurrently.

APPENDICES:

APPENDIX A: OPTIMA 430s data sheets and operating manual.

APPENDIX B: HDX/GE data sheets and operating manual.

APPENDIX C: Detailed description of 1) modifications made to the MR systems to accommodate whole body MRI of the neonate; 2) patient table developed to accommodate the smaller size of the magnet.

APPENDIX D: Previous work done in this area on the prototype neonatal MRI system.

APPENDIX E. MR System Safety Testing Data

APPENDIX F: Neonatal MRI images from the pilot study

APPENDIX G: MRI/Ultrasound Comparison Form

APPENDIX H: Head Ultrasound Procedures

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