CLINICAL USE OF A NEONATAL MRI SYSTEM

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Neonatal Intensive Care Unit (NICU)

ABSTRACT:

There are significant safety and image quality issues associated with transferring neonates from the Neonatal Intensive Care Unit (NICU) to the main Radiology Department for imaging in an adult-sized magnetic resonance imaging (MRI) scanner. For these reasons, the smallest and/or sickest neonates are typically precluded from receiving an MRI exam. The 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 (NICU MRI). To expand the imaging capabilities of the NICU MRI system, the measurement control electronics and operating system software of the FDA cleared 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). Further we have scanned almost 600 patients under a prior protocol (CCHMC Protocol 2011-2850) without an adverse event.

The present protocol seeks to allow continued performance of clinical MRI exams on the NICU magnet with improved administrative processes and procedures. NICU patients for whom an MRI exam is medically indicated will be recruited for the present study. Images will be obtained using both the FDA cleared OPTIMA NICU MRI platform and the integrated HDX/OPTIMA NICU MRI platform with the additional HDX images augmenting the OPTIMA images and contributing to diagnosis and guidance of subsequent clinical management. The specific MR imaging methods/procedures utilized will be determined by the type of exam to be performed and the medical indication. All of the MR images obtained will be reviewed by a board certified pediatric radiologist as part of clinical care and a clinical report will be generated and included in the infant's medical record.

PURPOSE OF STUDY:

The purpose of the present study is to continue clinical scanning on the NICU MRI with improved administrative processes and procedures, thereby making medically indicated, state of the art/high end MRI exams available to all infants treated at CCHMC.

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].

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, FDA cleared, 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). The HDX/GE platform is FDA cleared and is used to operate much of the GE MRI product line, including scanners used clinically at CCHMC. 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). This integration of the HDX/GE electronics and the OPTIMA hardware allows for advanced MR imaging more relevant to whole body and brain scanning.

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:

Details of prior pre-clinical animal testing 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). Further details about the NICU MRI system's safety testing are documented in the Previous Work In This Area section of protocol 2011-2045. The patient table, coils, specific absorption rate (SAR), acoustic noise, and peripheral nerve stimulation are all discussed. (See Appendix E: MR system safety testing data).

CCHMC IRB Protocol 2011-2045 was a pilot study including 15 neonates demonstrating safety and feasibility of the NICU MRI. 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.

Subsequently we have scanned nearly 600 patients on the NICU MRI without adverse event under CCHMC IRB Protocol 2011-2850.

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.

Inclusion criteria:

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

Exclusion criteria:

- Infants too large to fit in the customized NICU MRI system comfortably (generally 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 utilizing a feed and bundle technique. Occasionally, at the discretion of the

neonatologist, sedation will be necessary to obtain the imaging required for clinical diagnosis. This mirrors the process utilized on the conventional magnets in the Department of Radiology. The use of sedation and/or contrast is not part of the research.

Prior to MRI scanning, the patient's NICU care team will attempt to contact parent/LAR to communicate that a MRI has been ordered and provide information on the device, any potential risks and answer any questions the parent/LAR may have.

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.

Standard MRI safety screening will be performed by the MRI technologist per Department of Radiology practice. Screening will be documented according to standard Department of Radiology procedure.

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 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 images from a device that is FDA cleared. Additional sequences will be obtained with the HDX/GE platform. 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. If the patient remains stable throughout the MRI exam, an additional 10 minutes of scanning beyond the clinically indicated sequences may be obtained for ongoing sequence development and improvement efforts.

All coils used will be FDA cleared. Those not cleared will be submitted to the IRB and approved before they are used.

Monitoring of safety and tolerability:

Adverse events will be monitored during the MRI scan by the MRI technologist and the nurse/physician in the control room. Only adverse events that take place during MRI scanning will be recorded. Adverse events will be recorded on an adverse event log form kept in the MRI control room. In the event of an adverse event, the study team will be notified and a full report of the specific event will be submitted to the IRB promptly. 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 interpreted by a board certified pediatric radiologist or neuroradiologist and a standard report will be generated. This report will be included in the neonate's medical record and made available to the clinical team. 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.

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 conventional 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 related to maintenance of research records. 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 benefit their subsequent medical management. In addition, infants in the study may, 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 in research records 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 as these are examinations being performed for clinical indications. 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. The costs associated with additional imaging performed using the OPTIMA/HDX NICU MRI platform will be assumed by

the Department of Radiology. 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 NICU fellow or attending assigned to the patient (the fellow and attending are also part of the study team) will discuss the study with the parents/ LARs.

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.

CONSENT:

We are requesting a Waiver of Documentation of Informed Consent in accordance with 45 CFR 46.117 and 21CFR56.109 for this study. According to these regulations, the IRB may waive the requirements for investigators to obtain signed consent if one of two requirements are met. Our research study meets the second criterion that "the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (45 CFR 46,117)".

MR imaging is of no more than minimal risk for patients and is performed daily for clinical care of children in the CCHMC system. Other than potential administration of intravenous contrast (utilized only when clinically indicated), there is no instrumentation of, or intervention on, the patient as part of the MRI exam. Accordingly, specific procedural consent is not signed by LARs for the performance of MRI on conventional scanners (or administration of intravenous contrast) as part of normal clinical care.

In regards to 45 CFR 164.501, 164.508, 164.512(i), all protected health information generated as part of this study will remain confidential in accordance with CCHMC best practices. PHI, including but not limited to, date of birth, name, medical history, must be used to safely and adequately perform and document an MR exam. PHI related to this clinical MR study will not be disclosed to any other person or entity for additional research without a specific study IRB. All images and patient data are maintained securely in CCHMC's protected clinical PACS and in EPIC, both of which have electronic access controls. Specifically, CCHMC personnel must request access to these systems from their manager and CCHMC Information Services. Granted access is dependent on their institutionally assigned job description and credentials. Clinical PACS and EPIC are highly secure systems, hosted and supervised by CCHMC network security and are HIPAA compliant.

Patient identifiers will be available to the patients' care team as part of their clinical duties. It is not possible for the study team to withhold the MR images generated as part of this study from the patient's clinical staff because they rely on them for diagnostic

purposes and withholding these images would deny these patients potential clinical benefit. At no point will we destroy patient identifiers as they are the patient's clinical identifiers.

In many cases the parent/LAR is not on site when the physician orders an MRI and NICU staff have to reach them by phone. Transferring NICU patients to the main Radiology Department has specific risks related to difficulties with mobile monitoring, inadequate environmental controls (for a population susceptible to heat loss) and exposure to a general hospital population. All parents/LARs of prospective patients will have the NICU MRI study explained to them by their clinical care team who order the MR scan- the nature of the scan, financial costs, and possible adverse reactions, none of which differ from conventional MRI scanners. It will be made clear that participation in the study is voluntary.

NICU fellows or attendings, who are part of the study staff, will use the study information sheet provided and the verbal script below to communicate and obtain consent from parents/LARs.

The fellow or attending taking care of patient will call the parents/LARs and introduces him/her self. The fellow or attending then verifies that they are speaking with the correct parent/LAR using information. The physician will tell the parent/LAR that their child is scheduled to have an MRI of their brain/spine/abdomen/etc. and explain why the MRI is needed. Next, they tell them that they are calling the get their permission to use our NICU MRI. The script that follows will be used after the above introduction:

"An MRI machine uses a computer and a big magnet to take pictures. The magnet in our NICU scanner is much smaller than the magnets used in the MRI machines downstairs in the Radiology department. We are one of the only NICU's in the country that have MRI capability within the NICU as opposed to the hospital-wide radiology suite. Our MRI machine uses a smaller magnet than a typical MRI machine. Individually the MRI magnet and imaging software are FDA approved, but together as one unit they are not, therefore, I need your permission to use our NICU MRI for your child's study. We use the same process for obtaining the study and are able to get the same quality images using this machine as we would if your child were to have their MRI done in radiology, but with the added benefit of not having to travel off the unit. There are no additional risks by using the NICU MRI and in general we find it safer and more seamless to obtain the images when not having to travel off the floor. The same Radiologists read these images and we are able to bill your baby's insurance. There are no additional costs beyond the costs of an MRI in the big scanner downstairs. We will collect basic information about your child and the type of scan that was performed as part of quality control for the study. There are no known risks to the MRI scan itself and the MRI does not involve radiation. If you do not wish to have your baby's MRI performed in the NICU, we will schedule your baby to move downstairs for the MRI- sometimes it takes a little longer to schedule that. Do you have any questions for me at this time? ...Do you consent to having your baby's scan being done in our custom- built NICU MRI?"

A participant information sheet will be provided to parents/LARs. This information sheet serves as a study summary.

Non-English speaking participants will be consented using an interpreter. The interpreter will read the verbal script above to the family. The NICU fellow or attending consenting the parent/LAR will be present to answer any questions and to confirm the family understands the research. A witness (any available NICU staff) will be present to confirm the process has been completed. The fellow or attending will document consent has been obtained and that all questions have been answered, in addition to, the interpreter's name, ID, and credentials and the witness' name and credentials in the EPIC process note. This note will also be saved into the patient's research record.

This instance is rare. Under CCHMC IRB 2011-2850 we obtained consent from two non-English speaking parents/LARs on average per year. This is in comparison to the 110 English speaking parents/LARs on average per year.

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. The study PI will communicate regularly with the study coordinator and will review documentation and any AEs that have occurred.

All unanticipated problems and adverse event will be submitted to the IRB per institutional policy.

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

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