Exhibit C – SyMRI and Sickkids Project Plan

Reducing scan times and improving care through quantitative imaging: Evaluating SyMRI in pediatric populations

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Revision overview

New Time Frame – Until end of 2017 for additional recruitment
Expanded to include participants on Research MRI and CDIU MRI
Increase # of patients
+25 Neonatal
+75 All ages
Added Chris Macgowan as co-PI

1. Lay Summary

Typical magnetic resonance imaging (MRI) involves taking many images called 'contrasts' to look at the body in different ways. Standard scan settings are usually good enough for a radiologist to review. The best settings often change with the age of the patient and their health, and are time consuming to determine. Quantified imaging is an alternative to contrast-based imaging which explicitly measures tissue properties and can be used to create almost any contrast. This method of imaging has been held back by a lack of the right software. Synthetic MR Technologies has created a quantified imaging solution - **SyMRI** - to enable radiologists to acquire quantified images and always obtain the best contrast images.

2. Objective

The objective of this study is to evaluate SyMRI in a pediatric population to determine if Sickkids would be interested in purchasing this product / support Health Canada approval. Specifically, we are interested in determining if SyMRI is clinically useful:

- Is synthetic imaging quality comparable / better than conventional imaging?
    - Qualitative – Are radiologists more confident using synthetic MR vs conventional
    - Quantitative – Signal-to-noise (SNR) and Contrast-to-noise (CNR)
- To what extent can total exam times be reduced?
- Is the software user friendly and would our radiologists use it?

SyMRI will be integrated in future MR systems manufactured by GE and Philips. For GE, their next MR system software releases (DB25 and Signa Pioneer) will include SyMRI as a purchasable option – FDA approval is expected in Q2 2015. Philips is targeting Q2/Q3 2015 for releasing SyMRI on its 1.5T and 3T platforms. To evaluate this product without regulatory approval (considered a Class II medical device) an Investigational Testing Authorization (ITA) must be filed with Health Canada. Local REB approval is required as part of the ITA application.

3. Background

Typical clinical MR scanning requires the imaging of multiple contrasts (T1, T2, FLAIR) to provide radiologists with sufficient data for reporting purposes. However, these contrast images typically have no quantitative value and are defined by strict acquisition parameters that are not easily adjusted. Developmental changes or pathologies which affect tissue relaxation parameters often require non-standard parameters for optimal imaging. For example, T1 relaxation times in grey matter (GM) and white matter (WM) at 1.5T will range from 2000 and 3000ms, in very preterm born neonates at birth, but will decrease to 1100 and 800ms by adulthood. The two- to three-fold decrease in relaxation times, coupled with GM-T1 becoming longer than WM-T1 with age, necessitates dramatically different imaging parameters. These changes in T1 with age, and similarly with T2, vary by subject and are very difficult to determine *a priori*. Consequently, current practise is to set general parameters by approximate age group – Neonates (<1 mth), Infants (1mth-2yr), Adolescents (2yr-12yr), and Teenagers/Adults (13+). However, as both T1, and T2 continue to change with age, and may be affected by pathology, i) **image contrast using generic parameters is often sub-optimal** and ii) **total exam times may be increased** in an attempt to improve contrast by adjusting parameters on the fly.

An alternative approach to imaging specific contrasts is to directly quantify tissue parameters – T1, T2, Proton Density (PD) – and use these quantitative parameters to generate the desired contrast images after acquisition. In doing so, i) **scan times may be reduced** as there will be no need to 'guess' or adjust acquisition parameters, and ii) almost **any image contrast may be generated**. Clinical adoption of quantified imaging has been hampered by the lack of an elegant pulse sequence and appropriate software that is compatible with typical clinical workflow.

Synthetic MR Technologies is attempting to address this issue by providing the **software** and the **pulse sequence** (in partnership with the major MR manufacturers) to bring MR quantification into clinical usage. The MDME sequence aims to provide whole absolute quantification of T1, T2, PD and B1 inhomogeneity in **5 minutes** at typical clinical resolution (0.8 x 0.8 x 5mm). SyMRI software then allows a user to synthesize any almost image contrast (T1, T2, PD, FLAIR, IR, DIR, etc) by adjusting imaging parameters after the fact. Conventional T1, T2, and FLAIR acquisitions would take a minimum of 12 minutes, and may need to be repeated if image contrast is poor. Not only could **total exam times be reduced**, by taking image generation offline, but **scan quality can be improved**, by enabling the examination of various contrast images that otherwise would not have been obtained.

There is great potential for this solution at the Hospital for Sick Children. A significant portion of the brain imaging performed at Sickids involves neonates and infants, which pose a unique problem in that tissue contrast changes rapidly during this period (ideal sequence at 3 months, is less useful at 6 months). Consequently, image contrast and therefore quality is often sub-optimal. Furthermore, a combined T1, T2 and FLAIR sequence would **save at least 5 minutes** per subject. Time savings could be even greater as the need for repeat scanning due to poor contrast could be eliminated.

To explore this opportunity, Sickkids and SyMRI would like to sign an evaluation agreement in partnership with Philips and Siemens to trial the MDME sequence and SyMRI software. Philips would provide the pulse sequence. SyMRI would provide the software and technical support. Sickkids would test the sequence initially in small population of adults (6-10) and then acquire a large cohort of neonates, infants, adolescent, and teenagers.

From a regulatory perspective, SyMRI is considered a Class II medical device. To proceed with this proposal, Sickkids will be filling an application for Investigational Testing Authorization (ITA) with Health

Canada on behalf of Synthetic MR. This application requires REB approval, and as an unfunded study, the REB application requires scientific Peer Review.

Select Publications

- Ambarki K, Lindqvist T, Wåhlin a, et al. Evaluation of automatic measurement of the intracranial volume based on quantitative MR imaging. AJNR Am J Neuroradiol. 2012;33(10):1951–6.
- Blystad I, Warntjes JBM, Smedby O, Landtblom A, Lundberg P, Larsson E. Synthetic MRI of the brain in a clinical setting. Acta Radiol. 2012;53(10):1158–63.
- Vågberg M, Lindqvist T, Ambarki K, et al. Automated determination of brain parenchymal fraction in multiple sclerosis. AJNR Am J Neuroradiol. 2013;34(3):498–504.
- Warntjes JBM, Leinhard OD, West J, Lundberg P. Rapid magnetic resonance quantification on the brain: Optimization for clinical usage. Magn Reson Med. 2008;60(2):320–9.
- West J, Warntjes JBM, Lundberg P. Novel whole brain segmentation and volume estimation using quantitative MRI. Eur Radiol. 2012;22(5):998–1007.

4. Methodology

Eligible subjects (see below for criteria) will be identified by WL from patients scheduled for clinical neuro MRIs on a weekly basis. WL will approach eligible subject's parents / guardian the day of their scan to present the research study and to seek consent. Subjects who agree to participate in the study will receive an additional 5 minutes of scanning using the SyMRI pulse sequence. Their clinical scans will be review as per standard operating procedure.

Subjects enrolled in this study will have their conventional and SyMRI scans read by a radiologist/fellow trained to use SyMRI at a later date. The radiologist will alternate between viewing SyMRI or conventional MRI first for any given subject. They will be asked to rate the diagnostic utility of SyMRI as better, equal, or worse than conventional MRI. In addition they will record how long they spend review each set of images. Finally, all radiologists involved in this study will be asked to provide feedback with respect to the usability of SyMRI software.

5. Analysis

SyMRI will be primarily evaluated on its ability to generate clinically useful images, and if it can be used to reduce total scan times in all, or some, of the target age groups. A secondary output of this project will be to evaluate the usability of SyMRI software and determine if it could be reasonably integrated into a radiologist's existing workflow.

Clinical Utility – SyMRI's average rating as 'Better', ' Equal', or 'Worse' than conventional imaging will be tabulated from all reviewer responses. Assigning a value of 3, 2, and 1 respectively to these ratings – SyMRI is expected to average no lower than a 2.0 – at least equal to conventional imaging. Paired parametric (t-test) and non-parametric (wilcoxon signed-rank) statistical tests will be used to compare time spent using SyMRI vs Conventional MRI to determine if one approach is significantly faster than the other.

Quantitative Image Quality – Image SNR in WM/GM will be calculated and compared between conventional MRI and SyMRI (used to generate fixed / comparable contrasts). Paired parametric (t-test) and non-parametric (wilcoxon signed-rank) statistical tests will be used to evaluate if one approach is significantly better than the other.

Scan Time Reduction – Average scan time of SyMRI vs. Conventional MRI will be computed based on timing data stored in the MR images. A minimum of 5 minutes of scan time is expected be saved using SyMRI.

6. Budget

No funding is required for this study. Software and installation will be provided by SyMRI and Philips at no charge. Work completed by WL will fall under his existing responsibilities.

7. Project Overview

1) Evaluate product performance relative to conventional T1, T2, FLAIR, qT1 and qT2
   a) Preliminary evaluation – 6 adult volunteers (>18 years of age)
   b) Clinical Evaluation
      i) 25 neonates (<1 month of age)
      ii) 25 infants (1mth – 2 years of age)
      iii) 25 adolescents (2 – 12 years of age)
      iv) 25 teenagers (13-18 years of age)
2) Evaluation
   a) Scan Time Impact - Scan report forms, documenting time spent scanning SyMRI, vs conventional MRI.
   b) Quantitative – Comparison of conventional and synthetic MR images using Matlab.
      i) SNR, CNR. Repeatability of images.
   c) Qualitative – Train radiologists / fellows to use SyMRI software. Complete questionnaire with respect to experience working with software. Diagnostic quality of SyMRI image
3) Data to be provided by Sickkids to SyMRI
   a) 4 in-vivo clinical imaging datasets including conventional clinical and product protocol
      i) De-identified DICOM images including clinical interpretation and commentary
      ii) 2 neonatal/infant and 2 adolescent/teenager

8. Estimated Timelines / Milestones

1) Sequence delivery (Philips, SyMRI, Sickkids) – Q4, 2015
2) Software delivery / installation (SyMRI, Sickkids) – Q4, 2015
3) Adult acquisition and evaluation complete (Sickkids) – Q4, 2015
4) Clinical evaluation (Sickkids) – 5 neonates + 5 adolescents / month – Ongoing
5) Initial data sharing and commentary (SyMRI, Sickkids) – Q4, 2015
   a. 1 from neonatal/infant and 1 from adolescent/teenager provided to SyMRI
6) Clinical acquisition complete (SyMRI, Sickkids) – Q1, 2016
   a. 1 from neonatal/infant and 1 from adolescent/teenager provided to SyMRI
7) Product evaluations complete and provided to SyMRI (SyMRI, Sickkids) – Q1, 2016
8) Sequence delivery (Siemens, SyMRI, Sickkids) – Q1, 2017
9) Research Acquisition (SyMRI, Sickkids) – 2017
10) Clinical Acquisition (Philips, Sickkids) – 2017
11) Product evaluation (Sickkids, SyMRI, Siemens, Philips) – Q4 2017

9. Recruitment Considerations

Inclusion / Exclusion criteria
Any stable patient undergoing clinical MRI of the brain is eligible for this study. Only those patients where an additional 10 minutes of MR imaging would not be advisable (ie. unstable, implants) will be excluded.
Research patients undergoing research MRI of the brain for another study will be eligible. Only those subjects where an additional 10 minutes of MR imaging cannot be accommodated into their original booking will be excluded.

Risks and benefits to patients
There are no risks associated with SyMRI. The pulse sequence is a modified clinical imaging sequence and does not approach any scanner safety limits. For Philips, the sequence has been approved by the scanner manufacturers themselves and will be installed by their employees. For Siemens, the sequence will be obtained as part of a C2P agreement between Karolinska University Hospital and The Hospital for Sick Children. There is no possibility of adverse events beyond those associated with normal clinical MR imaging.

Patients involved in the validation of SyMRI may benefit from the improved diagnostic capabilities of SyMRI (custom image contrasts). This may eliminate the need for a repeat MRI session as required images may be generated through post-processing. Future patients would also benefit from reduced scan times.

Consent and data sharing
Parents / Guardians of eligible patients will be approached by WL on the day of their scan. The consent provides a lay summary of the study's rationale and objectives. SyMRI adds 5-10 minutes of scanning to the patient's MR session. There is no additional risk associated. Parents / Guardians may opt-in to share their child's data with SyMRI for evaluative purposes.

The scans for a limited number of patients (4) will be shared with SyMRI for evaluative purposes. Data will be de-identified and transferred using Sickkids' secure file transfer service according to hospital guidelines. SyMRI may not share this data with any other parties.

10. Legal

Data Transfer Agreement
SyMRI and Sickkids will sign a software evaluation agreement for this study. This agreement will cover the aforementioned objectives and timeline. Additional terms outline legal responsibilities for both parties. This document has been reviewed by legal teams for both parties.

Regulatory Approval
SyMRI has CE and ISO regulatory approval. Their product is currently undergoing regulatory approval through MR manufacturers (GE, Philips).