Work Statement # 21

This Work Statement, effective as of November 09, 2015 ("Work Statement #21 Effective Date"), is made by and between The University of Texas M. D. Anderson Cancer Center ("Institution") and the General Electric Company through its GE Healthcare business unit ("GE"), pursuant to the Research Agreement between GE, Institution, and The University of Texas Health Science Center at Houston dated December 22, 2010 ("AGREEMENT"). Upon signature by authorized representatives of the parties, this Work Statement is incorporated into the AGREEMENT as Work Statement #19 and the study hereunder is designated as a Research Project under the AGREEMENT.

1. Study: Ken-Pin Hwang, Ph.D. (hereinafter "Investigator") has proposed the conduct of a clinical Investigator initiated non-significant risk research study entitled "**Advanced Applications of Synthetic MR and MAGIC**", attached to and incorporated herein as Attachment A (the "Study"). The Study will utilize the GE Discovery MR750 3.0T, as identified in Attachments 1.2 and 1.4 of the AGREEMENT ("Device") and referenced in the MR Exchange Value required under Attachments 2 and 4 of the AGREEMENT.

2. GE Contact Information:
Praveena Gangakhedkar, GE Academic Research Programs Manager (Email: praveena.gangakhedkar@ge.com Phone: 281-536-0503) will be the primary contact for the Investigator for this Work Statement.

3. Objective: The objectives of the Study are set forth in Attachment A.

4. Study Responsibilities: Institution and Investigator are the Sponsor and Investigator, respectively, and as such are responsible for complying with generally accepted professional standards of care, good clinical practices and all applicable laws, rules and regulations ("Applicable Law"), including applicable requirements of the United States Food and Drug Administration ("FDA"). Institution shall, and shall cause the Investigator, to comply with all Applicable Law.

5. Regulatory: Institution shall obtain all authorizations and take all steps with relevant bodies and authorities as necessary for the conduct of the Study and this Work Statement. Institution certifies that it and Investigator are not debarred under subsections 306(a) or (b) of the Federal Food, Drug and Cosmetic Act (U.S.C. § 335 (a) or (b)) and that it/he will not use in any capacity the services of any person debarred under such law with respect to services to be performed under this Work Statement. Institution also certifies that it and Investigator are not excluded from any federal health care program, including Medicare and Medicaid.

6. Deliverables to GE:

6.1 Institution shall submit periodic reports to GE on the progress of the Study, with details as noted in the milestone table below and in Attachment A. Each report is due at the time interval from this Work Statement #21 Effective Date noted in the table below. GE reserves the right to request clarifying information with respect to the reports as reasonably required and Institution shall provide such information within thirty (30) days from the date of request. In the event the reports are not received in time, GE, in its sole discretion, may suspend the Study and all support as described herein, until such reports are received by GE.

6.2 Milestone Table

Milestone	Time	Deliverables
1	12 months	Progress Report Technical Products Scientific Publications (target: 1 scientific conference submission)
2	24 months	Final Report Technical Products Scientific Publications (target: 1 journal submission)

Description:

- **Progress Report**: A summary of progress toward objectives, including:

- Description of how any investigational devices/software have been used/tested to date
- Assessment of the *technical performance* (image quality, any problems encountered, etc.) and *clinical utility* of the investigational devices/software **and developed devices/software**
- Representative image data to support this assessment.

- **Final Report:** Final report shall be prepared that describes development and investigations including:
  - the details of technical methods and software developed, including what considerations were taken into account, what specifications were chosen, the theory of operation, and other details relevant to understanding the technical design;
  - the experimental methods used to investigate, optimize and test the design;
  - the results of the tests, including quantitative and/or image data as appropriate; and
  - discussion regarding whether the research goals were met, limitations of the software/algorithm design, limitations of the experimental methods, suggestions for future work, etc.

  Note: the report may refer to supplemental materials (e.g. publications, conference presentations, etc.) for details.

- **Technical Products**: Software, including source code, simulations, etc. to implement, simulate, test, etc. the methods developed.

  The following technical products are targeted to be complete at the following milestones:
  - **Milestone 1: Models for 2D MDME sequence with analysis.**
  - **Milestone 2: Models for all sequences with predicted optimal sub-sampling schemes. Any newly developed sequences, reconstruction code, and/or algorithms.**

- **Scientific Publications**: Copies of all papers, conference abstracts, conference presentations (e.g. slides or posters) describing the project (or use of the investigational devices/software in a larger study). If unpublished at time deliverable is due, an indication of when the paper/abstract/presentation will be submitted, presented or published.

7. GE Support:

7.1 The Investigator and Institution have proposed the costs associated with the conduct of the Study as identified in the Study Budget be identified as in kind research contributions of the Institution against the value of the MRI equipment (MRI Exchange Value) required under Attachment 4 of the AGREEMENT. GE and Institution agree that the Study Budget attached to and incorporated herein as Attachment B has been established and negotiated at arm's length, and is fair, reasonable and consistent with fair market value.

7.2 Institution will submit cost certifications ("Cost Certificate") to GE every six (6) months for all open studies under the AGREEMENT on or before 30 June and 31st December of each year of the AGREEMENT. Institution will also submit a final Cost Certificate within sixty (60) days of completion or termination of the Study. The Cost Certificate will detail all personnel who worked on the Study and all costs and expenses incurred up to the date of the Cost Certificate. Each Cost Certificate should include a certification by an authorized employee in the following form:

> I [*insert name of authorized employee*] certify that: (1) Institution maintains an accurate system for recording time/costs and expenses ("Costs") incurred on a study, (2) I have direct knowledge of all time/costs and expenses of the personnel who worked on this Study, (3) to the best of my knowledge the Costs detailed in this Cost Certificate are a true and accurate reflection of the costs and expenses actually incurred on this Study, (4) the Costs do not include any costs for scans or other testing that was covered by patient/subject insurance or other third party payors, (5) the Costs do not include any costs or expenses covered by any third party support arrangements.
> Signed:
> Name:
> Date:

7.3 The actual value of in-kind research services contribution attributed to such MRI Exchange Value will be determined every six (6) months upon receipt and acceptance by GE of the required Cost Certificate and Deliverables submitted by Institution.

7.4 GE Software: GE will provide Institution with certain software and source code referred to as, Compressed Sensing sub-sampling methods and reconstruction (collectively, the "GE Software"). Institution will maintain appropriate control and safeguards of the GE Software and will assure that the GE Software is not utilized except solely for Study purposes as specified the Agreement. Any other use of the GE Software is prohibited and constitutes a material breach of this Agreement. The GE Software and Device are and remain the sole property of GE. GE grants to Institution a limited, non-exclusive, non-transferable, revocable, terminable license to use the GE Software only for Study purposes as defined in the Agreement. Institution may not: (i) copy, sublicense, distribute, rent, lease, loan, resell, modify or translate the GE Software or create derivative works based thereon; (ii) directly or indirectly decompile, disassemble, reverse engineer or otherwise attempt to learn the source code, structure, algorithms or ideas underlying the GE Software; (iii) provide service bureau, time share or subscription services based on the GE Software; (iv) remove, obscure or modify any markings, labels or any notice of the proprietary rights, including copyright, patent and trademark notices of GE or its licensors; (v) electronically transfer the GE Software; or (vi) publicly release the results of any testing or benchmarking of the GE Software. GE and its licensors, as applicable, retain all ownership and intellectual property rights to the GE Software and documentation. No license rights are granted (whether by implied license or otherwise), to Institution, except as specifically provided in this Section. For the avoidance of doubt, this GE Software license will immediately terminate upon expiration or termination of this Work Statement. GE retains the right to terminate this GE Software license at any time and for any reason upon written notice to Institution. Should GE terminate this GE Software license, Institution will immediately remove the GE Software from the Device, if applicable, and immediately discontinue its use. The GE Software, together with any and all related documentation, including each and every part thereof, is provided AS IS. NO EXPRESS OR IMPLIED WARRANTIES, INCLUDING IMPLIED WARRANTIES OF NON-INFRINGEMENT, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE, APPLY TO ANYTHING PROVIDED BY GE HEREUNDER. GE MAKES NO COMMITMENT, EXPRESS OR IMPLIED, AS TO THE FUTURE AVAILABILITY OF THE GE SOFTWARE. Should the GE Software cause the Device to malfunction, GE will use commercially reasonable efforts to repair the Device according to the terms and conditions of the service agreement between GE and Institution covering the Device, provided the GE Software was used by Institution in accordance with this Agreement and the operator's manuals provided by GE regarding the use of the GE Software. Institution and Investigator recognize and agree that the GE Software is investigational and as such may be difficult and/or time consuming to repair. Institution also recognizes and agrees that GE may elect to replace defective GE Software with an alternative GE software, or GE may elect to terminate this GE Software license rather than repair or replace the defective GE Software or repair the malfunctioned Device. In the event Institution does not have a service agreement with GE covering the Device, GE shall endeavor to work with Institution's service provider to affect repairs, however any service provided by GE will be at its then-current standard applicable service rates.

7.5 Return of GE Software: Upon termination of the license to the GE Software license, Institution will promptly return the GE Software at GE's reasonable expense and per GE's reasonable instructions.

8. Transfer of Rights: No transfer or grant of rights under any patents or copyrights is made or is to be implied by any provision of this Work Statement other than those conferred through the AGREEMENT.

9. Confidentiality/Publication Review:

9.1 Any publication or presentation of results from this Work Statement is subject to the terms of the AGREEMENT. The parties agree to submit all manuscripts and abstracts resulting from this Work Statement to the other by way of their respective Authorized Representatives, at least thirty (30) days prior to submission for review, as provided in Article 9 of the AGREEMENT.

9.2 Institution agrees to acknowledge GE support and, as appropriate, GE resources as co-authors, in any presentations or publications resulting from work conducted under this Work Statement.

10. Term: The term of this Work Statement shall begin on the Work Statement #21 Effective Date and shall expire on November 30, 2016 unless terminated earlier in accordance with Article 13 of the AGREEMENT or unless extended by mutual consent of the parties.

IN WITNESS WHEREOF, the parties hereto have duly executed this Work Statement, as of the Work Statement #17 Effective Date.

GENERAL ELECTRIC COMPANY

By:_____
Sandhya Parameswaran
Research Manager – MR
GE Healthcare
Date: _____

THE UNIVERSITY OF TEXAS M. D. ANDERSON CANCER CENTER

By:_____
Chris McKee, MHA
Vice President, Business Operations
Date: _____

Read and Acknowledged by:

By: _____
Ken-Pin Hwang, Ph.D.
Investigator
Date: _____

Attachment A: Study Plan
Attachment B: Study Budget

Attachment B
Study Budget

Project Title: Advanced Applications of Synthetic MR and MAGIC

Institution: The University of Texas M.D. Anderson Cancer Center

Project Leader: Ken-Pin Hwang

Study Protocol Title(s): (Identify all protocol(s) - as identified to EC or IACUC - to be utilized to execute this Project Plan)

Protocol Title	Principal Investigator
2011-0542-02: "White Matter Matters: Clinical Use of Quantitative MR Imaging of Primary Brain Tumors to Characterize the non-contrast Enhancing T2-Hyperintense Tumor Environment"	Linda Chi, MD
.	.

Protocol Notes (If the Project Title is different from the Protocol Titles(s) submitted to the EC, or if the Study Protocol Principal Investigator is different from the Project Leader, please explain the relationship, e.g. project leader is sub-investigator. If multiple protocols will be utilized, describe how they relate to various aspects of the overall project design.)

The investigator is a sub-investigator on the protocol. The sequences to be modified or developed in this study match the type of sequences being investigated in this protocol.

Project Purpose & Objectives (Describe the purpose of the research, general hypothesis, and specific aims)

We hypothesize that information theory may be applied to develop a quantitative framework for estimating the efficiency of information acquisition (not simply data acquisition) for a multi-parameter mapping sequence. The approach will provide a measurement strategy to develop and optimize pulse sequences and reconstruction methods for synthetic MR imaging. Specifically, we aim to:

1. Develop an accurate signal model and numerical algorithms to quantify the information content of the current 2D MDME acquisition in the brain.
2. Develop and optimize sampling patterns and reconstruction techniques to reduce the overall acquisition time in the current 2D MDME sequence, and to achieve clinically acceptable acquisition times for a 3D technique.

Background & Rationale

Background (Describe the scientific context of this project, including previous work in this area)

The introduction of MAGiC and Synthetic MR on the GE platforms has generated considerable interest from the radiology community in its novel capabilities, including the generation of a wide variety of image contrasts from a single scan. However, limitations of the technique must also be understood and mitigated for the community as a whole to accept it in to clinical practice. These include a 2D acquisition technique that requires slice gaps due to the sensitivity of the technique to slice crosstalk, and a relatively long 5-6 minute scan. Also, the current technique is optimized for brain exams, but potential exists to extend this to other application areas where motion in not a concern.

Generally speaking, limitations on minimum scan time and/or resolution are highly dependent on the efficiency of the sequence. While efficiency is generally thought of as the ratio of sampling time to the total acquisition time, little can be done about prep pulse delay times or echo times without affecting the desired contrast of the sequence. An alternative way of assessing efficiency is to measure the amount of redundant information acquired by a sequence when we factor in the shared or correlated information in the full data set.

Advanced reconstruction methods have been applied to varying degrees of success. However, heuristically applying acceleration methods to the problem will not provide a quantitative understanding of how optimal these methods are, unless we first establish an understanding of the limitations of the information provided by the data. To do this we will apply concepts from information theory to predict these limitations and to quantitatively assess the performance of any acceleration method.

The reduction of uncertainty in one parameter due the knowledge of the other variables is known as Mutual Information. Information theory provides a rigorous mathematical framework to quantitatively identify optimal MR data that maximizes the information content of a physics based model of the acquisition. This can (1) provide a metric to evaluate any existing acceleration method, as well as (2) a strategy to optimize the sampling patterns or even the pulse sequence design to minimize acquisition of redundant information and reduce overall acquisition time.

Attachment B
Study Budget

Rationale (Given the background, describe the scientific value of this proposed project, and the potential value to GE)

In this study, we will be focusing primarily on acquisition techniques to accelerate or augment the Synthetic MR outputs. This will come from understanding the theoretical limits of the data and the application of these concepts to optimization of both 2D and 3D acquisitions, leading to faster 2D acquisitions and/or 3D acquisitions within a reasonable scan time.

Technical Development (If applicable, describe what is to be developed and the approach to development)

Existing physics models developed for T2* and chemical shift based temperature imaging (Madankan, Fuentes, et.al., TMI) will be adapted to assess the T1, T2, PD and B1 information required for synthetic image reconstruction from FSE-based sequences. These will be applied to the current 2D MDME acquisition to determine the theoretical minimum subsampled set of data required to reconstruct the same information as the full set of data. While similar methods of analysis have been applied to 3D parallel imaging methods as well as 4D k-t methods, their application to simultaneous multi-parameter mapping has been relatively unexplored.

Identifying the k-space locations and delay times with the most information content is equivalent with finding the measurement data that result in the greatest possible reduction of uncertainty in parameter (T1, T2, PD) estimates. Information theoretic approaches and the concept of mutual information have been used in numerous works for optimal measurements (Madankan, et al, American Control Conf. 2014, Krause, et al, J. of Machine Learning Research). Mutual information can be interpreted as the average Kullback-Leiber distance between the prior probability distribution of model parameters and the posterior probability distribution of the model parameters given the measurement data. In maximizing the mutual information, one inherently maximizes the difference between the prior and posterior distributions of the model parameters, thus leading to a better and more efficient data acquisition technique. Markov chain Monte Carlo methods and approximation techniques will be used to calculate the mutual information measures.

We will also assess current 3D multi-parameter mapping techniques to determine a suitable 3D solution for generating multi-contrast images. This may include extending the current FSE-based sequence to 3D Cube, or re-visiting previously proposed 3D techniques such as DESPOT. The emphasis will be on identifying robust techniques, and apply the same information analysis methods to determine their limits of acceleration. If one of the techniques is predicted to be sufficiently efficient, the sequence will be developed and assessed in human subjects.

Experimental Design (Note: If project is phased or segmented, describe the experimental approach to each phase or segment)

Subject Population (Describe the number of subjects and how they will be selected)

Volunteers and patients recruited for current SyntheticMR study, as well as possible clinical add-ons on DV25 scanners.

Data Acquisition Methods (Describe how data will be acquired)

Phase 1: Data will be acquired with the existing MAGIC/MDME technique, as available with the DV24 ATSM or in the product build on DV25. The current clinical protocol may be CV modified (without re-compilation) for full k-space sampling and/or customized delay times.

Phase 2: If warranted by analysis, the 2D sequence will be modified to acquire a mutual information maximized sub-sampling scheme. Also if warranted by analysis, a 3D sequence will be developed based on model predictions. Depending on the progress on previous goals, feasibility beyond neuro will be explored such as spine, MSK or pelvis.

Data Analysis Methods (Describe how data will be analyzed in order to draw conclusions)

Each sequence will be assessed for acquisition time and image quality, with full k-space sampling, current product ASSET sub-sampling, and the mutual information maximized sub-sampling scheme. Success is determined based on acceptable image quality within clinically feasible acquisition times.