SECTION I: Request

This is a formal request for the Utah CARMA Center to be formally recognized by the University of Utah as a large, collaborative medical and academic center whose focus is on comprehensive arrhythmia and research management. The CARMA Center has been operating since May of 2009 under the executive leadership of Dr. Nassir Marrouche, with the Senior Executive leadership of Dr. Lorris Betz, but now seeks a formal, large Center designation.

SECTION II: Need

Program Description

Atrial fibrillation (AF) is a growing problem in modern societies with an enormous impact on both short-term quality of life and long-term survival. Approximately 0.5% of people aged 50 to 59 have atrial fibrillation and in the population aged 80 to 89, 9% are afflicted with AF—and these prevalences are increasing. While many with the condition go untreated, AF is associated with an almost two-fold increase in the risk of mortality. AF patients experience a dramatically increased rate of stroke, from 1.5% for those aged 50 to 59 years to 23.5% for those aged between 80 and 89, a risk that, by contrast, decreases with age in the normal population. Treatment of AF represents a significant health care burden with the annual costs estimated at around $7 billion.

Restoring and maintaining normal cardiac rhythm remains one of the major goals in treating patients with AF. One treatment modality is a combination of electric shock (cardioversion) to restore regular cardiac rhythm and initiation of antiarrhythmic drugs, however, only 40-60% of the AF population is maintained in regular rhythm one year after such treatment. The treatment itself may also have serious adverse effects and drugs must usually be taken for the lifetime of the patient. Nevertheless, clinical trials have shown that maintaining sinus rhythm without the use of antiarrhythmic medication seems to be associated with increased survival. The inadequacies of drug-based treatments for AF have long been the major motivation for achieving more comprehensive understanding of the disease, its substrate and initiation, and then finding a truly alternative approach to maintain sinus rhythm and suppress AF.

The past decades have seen significant progress in understanding some of the underlying mechanisms that promote the occurrence and encourage the persistence of AF. That knowledge has led to a treatment paradigm with great promise but so far unfulfilled potential. The key finding that led to this therapy was the significant role of the pulmonary veins and the left atrium in initiating and maintaining atrial fibrillation. The aim of the resulting therapy has thus become to separate electrically the left atrium from the pulmonary veins, an approach known as pulmonary vein antrum isolation (PVAI).

Despite the fact that ablation, when successful, offers a complete and final cure, the success rate of ablation in maintaining regular sinus rhythm without the additional use of
antiarrhythmic medications still lies at 40-80%. Moreover, usage of ablation lags well behind the demand with a penetration level of less than 1%, in large part because of technical obstacles and incomplete management of complications.

These findings motivate a set of related goals that the CARMA Center seeks to address, including all aspects of the disease and that are highly translational in nature, both driven by and directed toward the assessment and management of patients with AF and other forms of atrial arrhythmias.

SECTION III: Institutional Impact

Center goals and mission, research plan, and academic and teaching contributions, and current structure plan

Center Mission: The mission of the CARMA Center is to provide worldwide pioneering leadership in advancing clinical treatments and research for cardiac arrhythmias, especially atrial fibrillation, a disease that causes both short and long term impairment in the quality of life for millions worldwide. The CARMA Center is advancing research to understand this disease and to improve medical techniques and interventions that greatly improve the lives of patients.

The Center casts a wide net, by inviting a diverse group of scientists and clinicians who are interested in partnering with the Center's research and clinical outcome goals. The Center creates novel opportunities for specialists from a wide range of fields, including Cardiology, Imaging, Biomarkers, and Biomedical Engineering and basic science disciplines to collaborate on investigations that advance the treatment of a disease that has a dramatic impact on societies across the world.

Ultimately, the CARMA Center will have achieved its mission when cardiac arrhythmia disease management teams have the ability to accurately diagnosis, treat, and cure the disease, allowing patients to return to healthy, productive lives.

Proposed Research Plan: The CARMA Center aims to lead the initiative to overcome the major obstacles that are responsible for the relative poor evaluation and management of atrial fibrillation by initiating and coordinating an interdisciplinary, international research effort to redefine the key characteristics of both the disease and its treatment. Challenges the center is focused on overcoming are:

A. Study the pathophysiology and genetics of the disease:
   1) Improve the state of understanding of the pathophysiology of AF through experimental studies and development of animal models of AF.
   2) Evaluate the co-morbidities of AF and other diseases, e.g., diabetes, coronary artery disease, heart failure, etc.

B. Develop techniques for personalized assessment of AF:
3) Evaluate patients for their risk and extent of AF using noninvasive approaches such as imaging and genetic analysis.

4) Develop image-based markers (cell/molecular targeting) to identify patients at high risk of stroke/death.

5) Develop methods to select best personalized treatment alternatives.
   a. Define the appropriate candidate for an ablation procedure
   b. Triage for other treatment approaches.

C. Develop techniques for personalized treatment of AF:
   6) Develop improved PVI techniques.
      a. Develop adequate real-time MRI catheter guidance.
      b. Develop real-time lesion detection and monitoring.

   7) Develop improved PVI assessment techniques
      a. Develop techniques to evaluate scar formation.

D. Enable multicenter research collaborations:
   9) Develop standardized imaging and image processing techniques

   10) Develop standardized information systems to capture and track patient information

   11) Develop and evaluate standardized patient management strategies

   12) Implement standards in an Internet based database system.

Essential to our goals is the novel use of medical imaging and image processing, including magnetic resonance imaging (MRI) and advanced visualization and computing in all stages of patient evaluation and treatment. MRI currently provides the only noninvasive means of assessing the tissue substrate that creates the “fuel” for AF and also the only means with the potential of determining success of the treatment. With suitable developments, it can also provide a means of real time guidance of the ablation procedure and thus has the potential to provide a complete means of management of the disease. Additional advances in the use of MRI based markers of fibrosis, inflammation, or tissue scar could dramatically improve the assessment of patients with AF, before, during and after their treatments. The hospital has been very supportive of this endeavour and recently opened the first-in-north-america joint electrophysiology/MRI lab.

**Academic and teaching contributions:** The CARMA Center fulfills an academic mission by providing an interdisciplinary training program for undergraduate, doctoral, and medical trainees in the School of Medicine, Bioengineering, (Medical) Physics, Radiology, and the School of Computing at the University of Utah and University Hospital. The academic goals of the Center are to leverage the existing outstanding interdisciplinary research environment at the University of Utah in order to create a uniquely multifaceted and comprehensive program in the understanding and management of atrial arrhythmias and especially atrial fibrillation. Such a Center will enable new funding proposals that require a comprehensive interdisciplinary approach such as NIH center, partnership, and program project grants. The center will create novel opportunities for specialists from a wide range of fields to contribute to the advancement of treatment of a major disease. The teaching opportunities will come through the creation of new, specialized courses or components of courses in cardiac imaging, electrophysiology, and image processing. We propose to create NIH training grant opportunities through
collaborative academic programs with the Departments of Bioengineering, (Medical) Physics, Radiology, and Internal Medicine and the School of Computing that will provide training in interdisciplinary science for undergraduate, doctoral, and medical trainees.

**Interactions with other academic units:** The interdisciplinary nature of the program and the inclusion of PI’s from multiple departments and colleges on the campus of the University of Utah will ensure a broad impact across many areas. Besides the obvious partners in medical imaging, radiology, scientific computing, bioengineering, and cardiology, AF has links to stroke and vascular disease, neurology, and genetics that link the center to collaborations across the entire campus.

**Structure and organization**

**Current Environment:** The current CARMA Center atrial fibrillation group consists of three principal investigators, all faculty at the University of Utah in a range of disciplines (Cardiology, Radiology, Bioengineering) and all experienced members and leaders of existing University Institutes and Centers (Utah Center for Advanced Imaging Research—UCAIR, Cardiovascular Research and Training Institute—CVRTI, and the Scientific Computing and Imaging Institute—SCI). These PI’s are supported by a team of approximately 30 clinicians, researchers, staff, and students.

The Center’s staff are organized into 4 main divisions: 1) Administration, Development, and Grant Support, 2) Electrophysiology (EP) Research, 3) Imaging Research, and 4) Clinical Research. While several of these individuals are already in place, as the center continues to grow, more of these positions will continue to be filled. However, we have identified the key figures in this organization that include the following (the list below includes those already hired into a position and proposed future positions):

- **Executive Director, Dr. Nassir Marrouche:** Executive responsibilities related to the center.
- **Director, Jeremy Fotheringham, RN, MHSA, JD:** to coordinate administrative activities, operations, development, grants management, and support infrastructure.
  - **Grants and accounting support** to carry out technical and clerical aspects of grant proposal preparation and submission. Eventually accounting and administrative assistance for managing the grant support.
  - **Clinical studies support, Mauricio Berdugo, MD:** clinical studies manager and study coordinator.
  - **Computer support, Thom Haslam:** dedicated systems support to ensure that data management is secure and coordinated and that all required HIPPA-related requirements are met.
- **Director, Electrophysiology (EP) Research, Chris McGann:** coordinate research activities in basic and applied electrophysiology
  - **EP faculty** with appointments in Cardiology, Bioengineering, and Physiology engaged in animal, human, and simulation studies.
• Experiment coordinator, Gene Payne: Lead experiment responsibilities including protocol development, safety, and planning
• Experiment technician, Chris Gloschat/Swati Rao: to provide support for experiments.
• Director, Imaging Research, Rob Macleod: coordinate both image acquisition and image processing research activities.
  o MRI physicist, Eugene Kholmovsky to carry out pulse sequence development and research.
  o Image processing faculty, Sathya Vijayakumar: Develop and test new image processing systems.
  o MRI technologist to support imaging studies.
  o Software engineers to coordinate all software development and maintenance.
  o Software developers to create and test computer code.
• Director, Clinical Research
  o Clinical research faculty to carry out research projects with clinical focus.
  o Clinical studies manager to organize and coordinate clinical studies.
  o Clinical study coordinator(s) to carry out direct management of clinical studies.
  o Clinical image processing to carry out image processing of clinical data.
• Postdoctoral and Clinical fellows are the engine that fuels any successful research endeavor and there is an urgent need for research associates with previous relevant experience and training
• Students, including graduate (PhD), undergraduate, and medical students already serve a crucial role in the research and clinical activities of the AF group and will continue to provide an invaluable resource as well as fulfill our academic obligation to enrich the education environment of the University.

SECTION IV: Finances

Current funding sources for the current research and development of the Center members are largely from industry (Siemens Medical Solutions, Surgivision, Biosense Webster—Johnson & Johnson) and seed grant support from the University of Utah. Members of the Center are actively pursuing NIH and American Heart Association support and will continue to seek external funding.

The Center also proposes a financial development campaign based on multiple private sources of support with the target of leveraging the outstanding clinical success of our approach to establish a significant base with which to pursue the goals described above. We are hosting a major event held at the hospital and the Eccles House on November 20th which includes several high-level donors. The donation target for this event is $5 million dollars, with a 2010 year goal of $10 million dollars, and by 2011 a total of $20 million dollars donated to the CARMA Center.
Other than the requested support for development activities, no other financial support is requested from the University of Utah.

The technical facilities on the University of Utah required for this Center are already outstanding and we plan to continue to make extensive use of imaging, experimental, and computational facilities at the partnering Centers and Institutes. We are also about to complete a dedicated multimodal interventional cardiac electrophysiology suite in the University Hospital that will contain all the relevant imaging systems, including interventional MRI, for evaluating and treating AF in experimental and clinical studies. We have also recently received dedicated office space in the School of Medicine and will require only remodeling support to maximize utility of this space as the physical home of the proposed Center. However, there is active pursuit of a much larger and more accommodating space for the rapidly growing CARMA Center team. In addition to general operations space, a requirement for continued success of the Center will be access to imaging facilities that support both human and animal studies.