1. **Project Title:** Multiscale modeling of inherited cardiomyopathies and therapeutic interventions (**PI's:** Kenneth S. Campbell and Jonathan F. Wenk)

2. **Summary:** Our project goal is to develop a predictive multiscale model of the heart that will improve understanding of familial cardiomyopathies and that can be used to help screen potential new therapies for cardiac disease. In the future, scientists and clinicians will be able to use the software to help optimize personalized treatment plans for patients who have different types cardiovascular disease. IMAG wiki.

3. **Details regarding Model Credibility plan following the CPMS Ten Simple Rules (TSR) format. It is requested that these details be presented as deemed appropriate for each modeling approach. This will be used to help define best practices for future reporting activities. These details should include:**

   A. **List of planned actions outlined in Model Credibility plan**
   Key experiments and their relationship to various model parameters are outlined in the table below.

Structural level	Time scale	Experimental data	Modeling approach	Associated model parameters
Molecular	ms	Kinetic and in vitro motility assays	MyoSim	Myosin rate constants
Cells	ms to s	Unloaded sarcomere shortening profiles, Ca^{2+} transients	MyoSim	Molecular parameters plus thin filament on/off rates, cooperativity, and titin-mediated stiffness
Tissue	ms to s	Force, tension recovery kinetics, force-velocity curves	Small-scale FE system	Cell-level parameters plus collagen-based stiffness
Organ	ms to s (single cardiac cycle)	Ventricular pressure and myocardial strain patterns	Organ-scale FE systems	Passive parameters, active force scaling coefficient, Windkessel model parameters
Organ/ Cells	Days to months	Ventricular geometry/ cell morphology	Growth and remodeling FE systems	Growth tensor $\mathbf{F}^{g}$; rate constants for sarcomere deposition and removal
Outline of experiments and link to models at multiple temporal and spatial levels				

   B. **Brief description of information gained by each credibility action**
   The molecular and cellular level experiments will provide insights on how the binding kinetics between actin and myosin are altered due to the genetic mutations associated with HCM. This information will be critical for refining and validating the behavior of the cell level computational algorithms. For example, we are implementing a framework that can accommodate cross-bridge schemes with any number of states. The experiments will help inform what states should be included to fully capture the nature of the disease and potential treatments.

The tissue level experiments will help bridge the gap to the organ level experiments, i.e., these will provide insights on how force generation in the myocardium affects ventricular performance and deformation. This will be critical for validating the organ level model to make sure it accurately couples all of the length scales.

Over the longer time scales, both organ and cell level experiments will help capture how function and geometry are affected by the disease and treatment. This information will inform the growth and remodeling algorithms that will be implemented into the model framework.

C. Actions and activities classified within the CPMS TSR framework (item-by-item summary table). If any of the TSR items are not being implemented/considered or additional items are being implemented, this information should also be explicitly stated

Rule 1 – Define context clearly.
We are developing, validating, and calibrating a model that uses data quantifying molecular-level myosin function to predict how hearts remodel over time. We will test the computational model initially using data from wild-type mice and from transgenic animals that develop cardiac hypertrophy because of a mutation in a protein that regulates myosin motor function. Additional tests will then be performed using drugs that enhance or inhibit myosin-level contractile function.

Rule 2 – Use appropriate data.
The outline of the data being collected is given in the table above. Our team is very interdisciplinary and has worked closely to develop the design of experiments. The specific experiments were chosen to directly inform key parts of the model framework. This will reduce the phenomenological nature of the model, and allow it to directly link model parameters to measurable quantities. Data collection at the molecular and cellular level will be overseen by the biophysicists on the team, while the tissue and organ level experiments will be handled jointly by the biophysicists and engineering personnel.

Rule 3 – Evaluate within context.
VERIFICATION: Numerical solutions will be verified and benchmarked at each stage of the development process against solutions from simplified systems which include ‘single element’ finite element (FE) models and analytical models (with closed form solutions). The modular structure of the code will provide additional flexibility in terms of debugging and solution verification. Stability analysis will be performed to determine critical time step requirements for convergence in our numerical models.

VALIDATION: The multiscale model spans from molecular to organ-level structural scales and encompasses timescales ranging from milliseconds to months. The project will produce experimental data at each of these levels, which directly relate to the model parameters (see table). The simulations can therefore be validated at each point by comparing computed predictions to analogous measurements. For example, at the cell level, unloaded sarcomere shortening profiles and Ca2+ transients generated by the MyoSim code will be calibrated against experiments from isolated cells to determine parameters such as thin filament cooperativity. At the organ level, P-V loops and myocardial strain patterns generated by ventricular FE models will be calibrated with experimental data from MRI to determine parameters defining the stress-strain relationship, as well as circulatory model parameters. Parameter estimation will be performed using robust numerical optimization techniques, which utilize hybrid methods (such as simulated annealing, genetic algorithms, and the successive response surface method) that perform both global and local searches of the parameter space.

Rule 4 – List limitations explicitly.
Any assumptions, simplifications, or limitations will be clearly outlined in the publications that are transmitted from this work. For example, the spatial resolution of the MRI data, with respect to the ventricular wall in mice, will be clearly stated as a potential limitation.

Rule 5 – Use version control.
We are currently using GitHub for our version control. This extends to three major thrusts in this project. (1) With respect to the post-processing of DENSE MRI data, we currently have a repository for updates to the MATLAB based code. (2) The source code for the new FEniCS implementation of the finite element code, with the general-state contraction law, are be updated (privately for now). (3) The cellular level code is also be tracked with version control.

Rule 6 – Document adequately.
We are currently dedicating a day each month where all personnel on the project who are doing code development get together and write documentation (within the code itself and external documentation, such as user manuals). This allows different team members to make sure that all of the pertinent information is being captured in a consistent way. In addition, experimental protocols are documented thoroughly and are made available through the lab website. This ensures a consistent approach by each person gathering data.

Rule 7 – Disseminate broadly.
We have presented our work at several conferences over the last year, as well as the 2018 IMAG/MSM Consortium meeting. We will continue to disseminate our work through conferences and publications. We will also

make data and models available through our team website, as well as GitHub repositories.

Rule 8 – Get independent reviews.
The project team is excited to work with IMAG Project Scientists and other members of the Multiscale Modeling Consortium to expedite rigorous third-party evaluation of the modeling approaches. As described above, experimental data and modeling software will be shared online as it is acquired and developed. The evaluators may therefore be able to perform some of their tasks remotely and independently. Other aspects will be performed more efficiently if the evaluators can interact directly with the project team. A portion of the project budget has therefore been allocated to pay for evaluators to travel to UK-Lexington each year to meet with the investigators, view experiments as they are being performed, and work with the resulting data to identify strengths and weaknesses of the credibility plan.

Rule 9 – Test competing implementations.
We are in the process of moving from the LS-Dyna finite element framework to FEniCS, which will allow the code to truly be freely available. The current implementations in LS-Dyna have been validated thoroughly with previous experimental data. As we build up capabilities in FEniCS, we will compare to the previous implementation to confirm results. This will also be done with small scale simulations, which can be compared to output from the MyoSim code.

Rule 10 – Conform to standards.
As we move forward, we will migrate to a standard input file format, which can be more easily used by other investigators. For example, we are considering using XML as the input format for our computational tools.

D. Description of how the planned activities will lead to a credible model

If we are collecting experimental measurements in a consistent manner, this should lead to reproducibility in the experimental data. If we use reliable data as a means of validating the computational modeling algorithms, which have direct links between model parameters and experimental measurements, then the final resulting models should be able to accurately capture multi-scale behavior.

E. Progress to-date and plans for the next reporting cycle (6 months). What has been achieved since last reporting?

During this reporting period we have completed the implementation of a 3-state model of myocyte contraction, which captures length-dependent activation. This is due to the implementation of a “super-relaxed” state for myosin, which is a recent discovery and is a hot topic within the biophysics community. Adding this capability to our modeling scheme will enhance

accuracy. We are currently in the process of preparing this manuscript. We have also published 6 journal articles, which are listed in PubMed.
In terms of the next reporting cycle, we will ramp up efforts on data collection (spanning all scales) and will begin validating the new implementation in the FEniCS framework. This will give more versatility in terms of coupling and provide an open-source code for other researchers to use.

4. **Issues/concerns identified as critical or problematic to achieve the standard of credibility set by MSM Consortium.**
   We have only just completed the first year of this project. As of now, we have not identified any issues related to the standard of credibility.

5. **What other factors, if any, contribute to credibility but cannot be reported within the TSR structure? In requesting this information, we seek to identify credibility activities/issues and appropriate ways to report them at upcoming IMAG/MSM meetings.**
   None have been identified yet.