MODEL CREDIBILITY PLAN

The multiscale model proposed in this U01 application uniquely couples three modeling approaches into a combined simulation framework. We have budgeted funds for two third-party MSM community members to extend their stay by a day either before or after the MSM Consortium meeting to travel to the University of Virginia (which is a 2-hr drive from Washington D.C., where the MSM Consortium meetings are likely to be held), so that they can have a day-long meeting with the PD/PIs and provide feedback and advice to the team once per year. During these meetings, will report on the results of our model credibility assessment efforts in five key areas that we will be continuously evaluating throughout the development and execution of the multiscale model, four of which are described in the PAR (*Verification*, *Validation*, *Uncertainty Quantification & Sensitivity Analysis*, and *Documentation of Limitations*). We have also defined one additional aspect of model credibility that we think is critical to assess for our project: *Evaluation of Clinical Credibility.*

(a) Verification: Our proposed multi-scale simulation framework leverages two key existing software programs: NetLogo (https://ccl.northwestern.edu/netlogo/) and FEBio (http://febio.org). Both software programs are highly developed, and both have internal verification test models. Our simulation framework will take the form of Pearl scripts and C++ code that makes calls to both NetLogo and FEBio, abiding by stringent coding and documentation standards. We will develop a set of verification models for the combined simulation framework, with will include simple finite-element and agent-based models. These models will be used to assess convergence with respect to the key tolerances (described in the Approach). All of these verification models will be documented and provided with the developed code as part of our model and data sharing activities, and we will ask our MSM external evaluators to independently evaluate them.

(b) Validation: The research plan describes multiple levels of and methods for experimental validation of the model. Since our approach involves integrating multiple component models (macro-scale tissue models, micro-mechanical models, and agent-based models), we describe a set of validations that first validates each of these model components independently, secondarily validates individual couplings, and finally validates the fully coupled simulation. We will start by validating against data that we will generate using the *mdx* mouse model of muscular dystrophy, which allows us full and direct access to measurements of key parameters. We follow this with scaling and validation with parameters that are measurable in patients with DMD. We deem a model prediction of a particular quantity to be "valid" if the prediction falls within the 95% confidence interval of experimental measurements. We will share all of our validation efforts with our external visitors during the yearly visits, ask them for critical feedback, and integrate their feedback as we move forward.

(c) Sensitivity Analysis: We appreciate that the complexity of our multiscale model presents a challenge for robust uncertainty quantification and sensitivity analysis. In their specific modeling domains, both PIs have extensive experience with using sensitivity analysis to test, refine and validate models, reveal novel insights, and guide future experiments. In order to address the new computational challenge of performing sensitivity analysis of simulations that unite both deterministic (finite-element) and stochastic (agent-based) models, we will explore the use of recent developments that provide more efficient uncertainty quantification methods for deterministic problems, such as adaptive collocation methods for deterministic simulations and Markov-chain Monte-Carlo methods stochastic simulations. We will present and seek feedback from our external evaluators regarding the methods we use for our sensitivity analysis, and we will learn from and adopt best practices from the MSM community.

(d) Documentation of Model Limitations: The PD/PIs share the philosophy of consistently documenting "failed" simulations; in fact, we use a shared server for models and simulations, and we have a specific folder called "simulation explosions". We acknowledge that these failed simulations provide critical information regarding the limitations of our simulations and refine understanding of their applicability. We plan to document and share these failed simulations with the broader community, and highlight them to our external evaluators. In our recent publications, we have discussed model failures and what we have learned from them so that the community may also benefit from appreciating the limitations of our modeling approaches.

(e) Evaluation of Clinical Credibility: It is very important that our models are evaluated in a way that ensures their credibility with the clinical audience. For example, while our parameters may be validated and we understand the sensitivities, our predictions may still not be consistent with clinicians' observations. We will address this limitation by having consistent interactions with co-I Dr. Scharf, as well as the broad clinical community of muscular dystrophy. We plan to (i) present our findings regularly at the Pediatric Ground Rounds at UVA, and (ii) visit neighboring muscular dystrophy centers to present our work and hear from clinicians and therapists regarding the relevance of our findings, (iii) present our work at Muscular Dystrophy conferences.