Establishing Credible Practice Guidelines for Simulation-Based Medicine

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Presentation Outline

• Background on the Committee
• Committee’s definition of “Simulation”
• The Committee’s charge
• Current goals and activities of the Committee
• Real-world Examples of credible practice
• Future work
• Open discussion
BACKGROUND

• Computational modeling and simulation (M&S) methods have substantial potential to support research, clinical decision and education in healthcare

• Government agencies and industry are making substantial investments on R&D activities in simulation-based medicine and notable discoveries are being made

• Common practice guidelines do not exist to ensure these tools are appropriately applied
BACKGROUND

To bridge this gap, the

Committee on Credible Practice of Modeling & Simulation in Healthcare

was established under

IMAG & Multiscale Modeling (MSM) Consortium
**DEFINITION OF SIMULATION**

Credible Practice of Modeling & Simulation in Healthcare

*computational solution of models* to quantify descriptive and predictive metrics of system(s) of interest; including related post-processing efforts to calculate these metrics from raw analysis results
CHARGE: OVERVIEW

GUIDELINES & PROCEDURES
For credible practice in computational medicine by leveraging readily available techniques, and to define novel translational workflows to enhance credibility practice.

DEMONSTRATE WORKFLOWS
By conducting studies for the implementation of novel credibility assessment procedures, and by disseminating examples of credibility assessment.

CONSISTENT TERMINOLOGY
To unify the use of M&S vocabulary for clear communication across a variety of disciplines and stakeholders in the field.

PROMOTE GOOD PRACTICE
By bridging synergistic activities of establishing confidence in simulation-based medicine conducted by M&S communities, as well as conducting outreach activities.

END PRODUCT
I. “Guidelines for Credible Practice of M&S in Healthcare”
II. Proposed model certification process
III. Identify new areas of research to advance I & II
None of us are experts in everything. We need to learn from each other.

Credible practice of modeling and simulation in healthcare requires ongoing inclusive communications to establish adaptive workflows that can be utilized broadly.
**CHARGE: IMPLEMENTATION STRATEGY**

## Committee Executive Members (Execute & Charge)

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Ahmet Erdemir, Ph.D.</td>
<td>Co-Chair</td>
<td>Cleveland Clinic</td>
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<tr>
<td>Lealem Mulugeta, M.Sc.</td>
<td>Co-Chair</td>
<td>Universities Space Research Assoc.</td>
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<tr>
<td>Gary An, MD</td>
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<td>University of Chicago</td>
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<tr>
<td>Jacob Barhak, Ph.D.</td>
<td></td>
<td>Independent</td>
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<tr>
<td>Joy Ku, Ph.D.</td>
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<td>Stanford University</td>
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<tr>
<td>Marc Garbey, Ph.D.</td>
<td></td>
<td>University of Houston</td>
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<tr>
<td>William Lytton, M.D.</td>
<td></td>
<td>Kings County Hospital Downstate Med. Center</td>
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<tr>
<td>Tina Morrison, Ph.D.</td>
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<td>FDA</td>
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<td>Jerry Myers, Ph.D.</td>
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<td>NASA</td>
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<td>Lu Tian, Ph.D.</td>
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<td>Stanford University</td>
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## Advisory Council (Review & Advise)

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<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Jeffrey Bischoff, Ph.D.</td>
<td></td>
<td>Zimmer</td>
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<tr>
<td>David Eckmann, M.D., Ph.D.</td>
<td></td>
<td>University of Pennsylvania</td>
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<tr>
<td>Ronald Germain, M.D., Ph.D.</td>
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<td>NIH</td>
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<tr>
<td>Anthony Hunt, Ph.D.</td>
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<td>University of California, San Francisco</td>
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<tr>
<td>Martin J. Steele, Ph.D.</td>
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<td>NASA</td>
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<td>Donna R. Lochner</td>
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<td>FDA</td>
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<tr>
<td>James Thomas, M.D.</td>
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<td>Cleveland Clinic</td>
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<tr>
<td>Vasilis Marmarelis, Ph.D.</td>
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<td>University of Southern California</td>
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<tr>
<td>Grace Peng, Ph.D.</td>
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<td>NIH</td>
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<td>Pras Pathmanathan, Ph.D.</td>
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<td>FDA</td>
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<tr>
<td>Wing Kam Liu, Ph.D.</td>
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<td>Northwestern University</td>
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<tr>
<td>Marlei Walton, Ph.D.</td>
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<td>Wyle Science, Technology and Engineering Group</td>
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Interagency Modeling and Analysis Group (IMAG) & Multiscale Modeling Consortium (MSM)

The Committee is divided into three Task Teams that represent the fundamental areas that are significant to our primary aims.

This team-based structure helps to:

- Establish a balanced representation of the interests and perspectives of the different stakeholders
- Bridge synergistic activities in simulation-based medicine throughout the M&S communities
The Committee’s primary deliverable by the end of the first two year term (03/2015) is to establish, “Guidelines for Credible Practice of Modeling and Simulation in Healthcare”

**Goal Oriented Activity:** The CPMS Task Teams were charged to identify ten key elements or simple rules of credible practice in order to establish a foundation from which the “Guidelines for Credible Practice of Modeling and Simulation in Healthcare” can be developed.

To initiate the Ten Simple Rules task, the following 26 simple rule candidates were initially generated and surveyed internally by the Committee.

<table>
<thead>
<tr>
<th>ONGOING: TEN SIMPLE RULES OF CREDIBLE PRACTICE</th>
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<tr>
<td>To initiate the Ten Simple Rules task, the following 26 simple rule candidates were initially generated and surveyed internally by the Committee.</td>
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</table>

- Use version control
- Use credible solvers
- Explicitly list your limitations
- Define the context the model is intended to be used for
- Define your evaluation metrics in advance
- Use appropriate data (input, validation, verification)
- Attempt validation within context
- Attempt verification within context
- Attempt uncertainty (error) estimation
- Perform appropriate level of sensitivity analysis within context of use
- Disseminate whenever possible (source code, test suite, data, etc)
- Report appropriately
- Use consistent terminology or define your terminology
- Get it reviewed by independent users/developers/members
- Learn from discipline-independent examples
- Be a discipline-independent/specific example
- Follow discipline-specific guidelines
- Conform to discipline-specific standards
- Document your code
- Develop with the end user in mind
- Provide user instructions whenever possible and applicable
- Practice what you preach
- Make sure your results are reproducible
- Provide examples of use
- Use traceable data that can be traced back to the origin
- Use competition of multiple implementations to check and balance each other
### Consolidated & Rephrased Rules

<table>
<thead>
<tr>
<th>#</th>
<th>Rule</th>
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<tbody>
<tr>
<td>1</td>
<td>Plan and develop the M&amp;S with clear definition of the intended purpose or context, and with end-user input</td>
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<tr>
<td>2</td>
<td>Document the your code and the M&amp;S (domain of validity/invalidity, intended use, user guide, etc), and make your code readable</td>
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<tr>
<td>3</td>
<td>Use version control</td>
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<tr>
<td>4</td>
<td>Test the M&amp;S Appropriately within Context (V&amp;V, UQ, sensitivity analysis (SA), test cases)</td>
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<tr>
<td>5</td>
<td>Use appropriate data</td>
</tr>
<tr>
<td>6</td>
<td>Disseminate whenever and whatever possible</td>
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<tr>
<td>7</td>
<td>Explicitly list the limitations of the M&amp;S</td>
</tr>
<tr>
<td>8</td>
<td>Adopt and promote standard operating procedures</td>
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<tr>
<td>9</td>
<td>Use competition of multiple implementations to check and balance each other</td>
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<tr>
<td>10</td>
<td>Make it easy for anyone to reproduce and/or falsify your results</td>
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<tr>
<td>11</td>
<td>Use traceable data that can be traced back to the origin</td>
</tr>
<tr>
<td>12</td>
<td>Define your evaluation metrics in advance</td>
</tr>
<tr>
<td>13</td>
<td>Have the M&amp;S reviewed by independent users/developers/members</td>
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These results will be analyzed and reported in more detail in an upcoming presentation at the 2014 ASME V&V Symposium in May.

Simulation-Based Healthcare Community Survey: To ensure that we capture the perspectives and interests of the global stakeholder community, we are preparing to launch a public survey of the new 33 simple rule candidates (increase due to internal survey results)

Survey of Models: To complement the survey, we are also conducting a survey of computational models to develop a better understanding of the needs and successes of different types and applications of M&S in healthcare

How can the SSH Community Participate?
• We strongly encourage the SSH community to participate in and promote the survey
• Contribute M&S examples that may help us better understand the needs and successes of different types and application of M&S within the SSH community
Upcoming: Ten Simple Rules, Guidelines & Cert.

Community Generated Ten Simple Rules

I
II
III
IV
V

VI
VII
VIII
IX
X

Guidelines for Credible Practice of M&S in Healthcare

Proposed Model Certification Process
**Example: Fractional Flow Reserve - CT**

<table>
<thead>
<tr>
<th>Description</th>
<th>Credibility Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intended use:</strong> Computes Fractional Flow Reserve (FFR) from non-invasive computed tomography images.</td>
<td>Used clinical studies specifically designed to evaluate the efficacy of the model for non-invasive cardiac diagnostic relative to the traditional invasive FFR</td>
</tr>
</tbody>
</table>
| **Limitations:** Clinical studies assess only the accuracy of the FFR<sub>CT</sub> quantity for coronary arteries | • HeartFlow NXT Study (2013) – 254 patients  
• DeFACTO Study (2012) – 252 patients  
• DISCOVER-FLOW Study (2011) – 103 patients |

### Appropriate Application
- Determining FFR<sub>CT</sub> for clinical decision-making purposes in terms of coronary artery disease
- Suitable for teaching purposes centered around FFR (and FFR<sub>CT</sub>)

### Inappropriate Application
- Computing FFR<sub>CT</sub> for diagnosing of other parts of the vasculature
- Utilizing quantities from the simulation other than FFR<sub>CT</sub> (e.g., pressure, wall shear stress) for clinical decisions
**Intended use:** Probabilistic risk assessment of bone fracture due to bone changes due to zero-gravity exposure – analyses may be run for spaceflight or terrestrial scenarios

**Limitations:**
- Small n - “Attributable” data for model development
- Uses DXA BMD, which has a limited correlation to bone strength or [resistance to fracture], and bone quality

**Description**

**Credibility Assessment**

Compared to two published data sets that are considered to be among the latest state of knowledge in bone loss and risk of fracture

- Development and Validation of a Predictive Bone Fracture Risk Model for Astronauts, Annals of Biomedical Engineering, 2009, Vol. 37, Number 11, 2337-2359

**Appropriate Application**

Provide supporting evidence for:
- Bone fracture risk due to spaceflight related bone loss in terrestrial and spaceflight environment
- Injury criteria definition: additional for fitness of duty evaluations for spaceflight, and injury loading thresholds
- Changes to inflight injury likelihood resulting from exercise or pharmaceutical countermeasures to bone loss

**Inappropriate Application**

- As a sole source of evidence to make decisions regarding bone fracture risk – credibility level is not sufficient for this
- Predict changes in bone volumetric density or architectural changes – µQCT and finite element methods are required for this
**Example: Gross Cardiovascular Physiology**

<table>
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<tr>
<th><strong>Description</strong></th>
<th><strong>Credibility Assessment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intended use:</strong> Education model to teach medical students about the general response of the cardiovascular system to various physiologic stresses, and administration of various interventions</td>
<td>• Verification against simple test cases</td>
</tr>
<tr>
<td><strong>Limitations:</strong> Assumes average adult male between the ages of 25 and 55, weighing 180 lbs, and 5' 9'' tall</td>
<td>• Face/qualitative validation against literature data by physicians and physiologists for general trends in physiologic responses</td>
</tr>
<tr>
<td><strong>Appropriate Application</strong></td>
<td>• Numerical stability and sensitivity analysis were not performed</td>
</tr>
<tr>
<td>• A teaching tool to provide very high level insight of how the cardiovascular system may respond to various stressors and interventions built into the simulation environment</td>
<td>• Historical development data and versions were not documented</td>
</tr>
<tr>
<td>• The educator should emphasize the simulations should be used as a supplement and not a replacement of their core curriculum</td>
<td><strong>Inappropriate Application</strong></td>
</tr>
<tr>
<td></td>
<td>• Conducting simulation scenarios that violate the primary assumptions</td>
</tr>
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<td></td>
<td>• Simulations of other physiologic systems</td>
</tr>
<tr>
<td></td>
<td>• Attempting to use the model for research or clinical purposes; credibility assessment is not sufficient for these kinds of applications, and it was developed for teaching purposes</td>
</tr>
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**Note:** This is a generalized example based off of a real use case of an educational model.
Goal: A Common Language Across Disciplines

**Goal Oriented Activity:** A glossary of terms is being generated on the Committee’s to help unify the use of M&S vocabulary across a variety of disciplines and stakeholders in the field.

We strongly encourage all stakeholders (e.g. SSH community) to help establish these terms and definitions by visiting: [http://wiki.simtk.org/cpms/Glossary_and_Definitions](http://wiki.simtk.org/cpms/Glossary_and_Definitions)

**Example**

![Example Image](image-url)
Goal: Adoption of Guidelines by Stakeholders

Goal Oriented Activity: We are taking every opportunity to engage and strongly encourage the global stakeholder community, such as the Society for SSH, to actively contribute to these efforts to ensure that the guidelines established capture the primary interests of the computational medicine community.

Open discussions and contribution to activities via:

- Wiki pages
- Discussion forum
- Meeting minutes
- Subversion repository access of all presentations, abstracts and posters

URL: https://simtk.org/home/cpms
**Future Work**

- Launch public survey to the global community (~3 months) – Projected launch date: ??/2014

- Analyze data, and publish results in PLOS Computational Biology in the form of “Ten Simple Rules of Credible Practice of M&S in Healthcare” – Estimated submission date: ??/2014

- Develop and publish the “Guidelines for Credible Practice in Modeling & Simulation in Healthcare” based off of the Ten Simple Rules – Estimated completion date: 03/2015
• What are the areas that are most important to you in simulation-based healthcare?

• Have we’ve missed something?

• What are the challenges you face in applying simulations effectively to educate the healthcare practitioners?

• Are there any use cases you want to discuss with us?

Please take advantage of the survey, public forum and wiki site to continue this conversation with us. The guidelines will ultimately belong to you, so we want to hear from you!
BACKUP SLIDES
**Credible** Practice of Modeling & Simulation in Healthcare

**dependable** with a **desired certainty level** to guide research or support decision making within a prescribed application domain and intended use; establishing **reproducibility & accountability**
Credible Practice of Modeling & Simulation in Healthcare

any activity involving development, solution, interpretation and application of computational representation of biological, environmental and man-made systems and their interaction thereof
Credible Practice of **Modeling** & Simulation in Healthcare

specifically *computational modeling*; virtual *representation* of system(s) of interest in a usable form in order to provide *descriptive* and *predictive* metrics for timely and systematic exploration of the system(s)
any activity involving development, maintenance, advancement, or administration of medical care; including research, diagnosis, risk assessment, prevention, therapy, rehabilitation, surgery, intervention design, and regulation
Modeling for Coronary Artery Disease Diagnostics

- Fractional Flow Reserve (FFR)
  - Current gold standard in assessing coronary artery disease
  - Invasive procedure
- Heartflow’s FFR$_{CT}$ technology computes FFR from non-invasive computed tomography images

Video from http://heartflow.com
**Overview of FFR\textsubscript{CT}**

- **Computed tomography angiography imaging**
- **Construct geometric model of main vessels of interest**
- **Discretize model into mesh for computation**
- **Model conditions at inlets and outlets of geometric model**
- **Computational fluid dynamics used to compute velocities and pressures, from which FFR\textsubscript{CT} can then be derived**

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Taylor, CA, Fonte, TA, Min, JK, “Computational Fluid Dynamics Applied to Cardiac Computed Tomography for Noninvasive Quantification of Fractional Flow Reserve,” 2013, JACC, 61(22):2233-2241
Building Confidence in the Model

• Started out with simple, “easy-to-test” *in vitro* model over 10 years ago
• Methods developed and tested to address limitations in the interim
• Assessing what model can be used for
  – Original idea: prediction of surgical bypass surgeries
  – Recent clinical studies assess technology for coronary artery flow, not necessarily applicable to other parts of the vasculature

(to add: graph of results from...)
What can we do to estimate astronaut risk of fracture?

Real and Present Concern: Skeletal Fracture
- Weakened bones
- Unique and off-nominal loading states

Lack of In Flight Injuries
- Predictive data is limited

Fracture risk
- Likelihood (unknown) + Severity (known)

Our Question is:
- What is the fracture likelihood in space (ISS, Orion) and on planetary activities (Moon and Mars)?
- Can such assessments be extended to the BMD recovery period after return?
THE LOADING ENVIRONMENT

Micro-g Translation

Stance
Walking
Ladder/Stair
Ascent/Decent

“Drop Landing”

Lateral/Posterolateral Fall Impacting the Hip Or Abnormal Lifting
Model Validation and Predictive Results

- Although femoral neck fracture is of high concern
  - Least likely location of fracture
- Wrist most likely fracture location

Nelson et al., Development and Validation of a Predictive Bone Fracture Risk Model for Astronauts, Annals of Biomedical Engineering, Vol 37, Number 11, 2337-2359