



CREDIBILITY OF COMPUTATIONAL METHODS IN HEALTHCARE: A COMPARISON OF COMMUNITY- BASED STANDARDS AND GUIDELINES

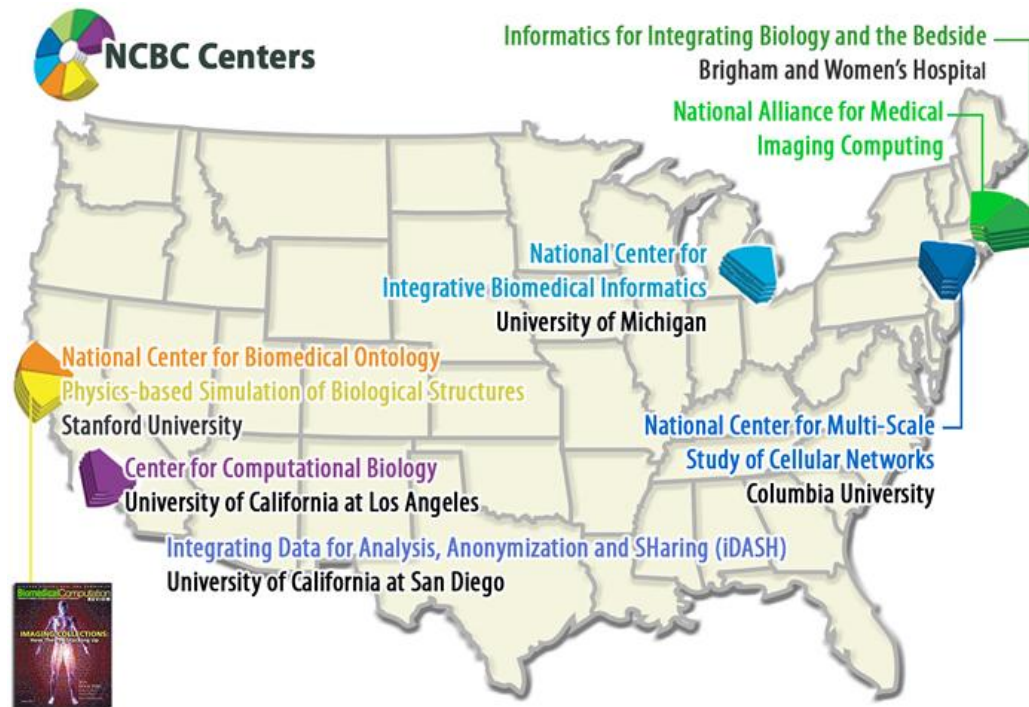
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D. Lochner¹, W.W. Lytton¹, V. Marmarelis¹, J.G. Myers¹, G. Peng¹, M.J. Steele¹ and M. Walton¹

1. IMAG/MSM Committee on Credible Practice of M&S in Healthcare
2. ASME V&V40: Verification and Validation in Computational Modeling of Medical Devices

*ASME Verification and Validation Symposium
Las Vegas, Nevada May 18-20, 2016*

BACKGROUND

- Computational modeling and simulation (M&S) methods have substantial potential to support research, clinical decisions 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



adapted from [NCBC website \(2014\)](#)



**Am I applying
credible practice?**

Common practice guidelines do not exist to ensure that appropriate credibility processes are followed

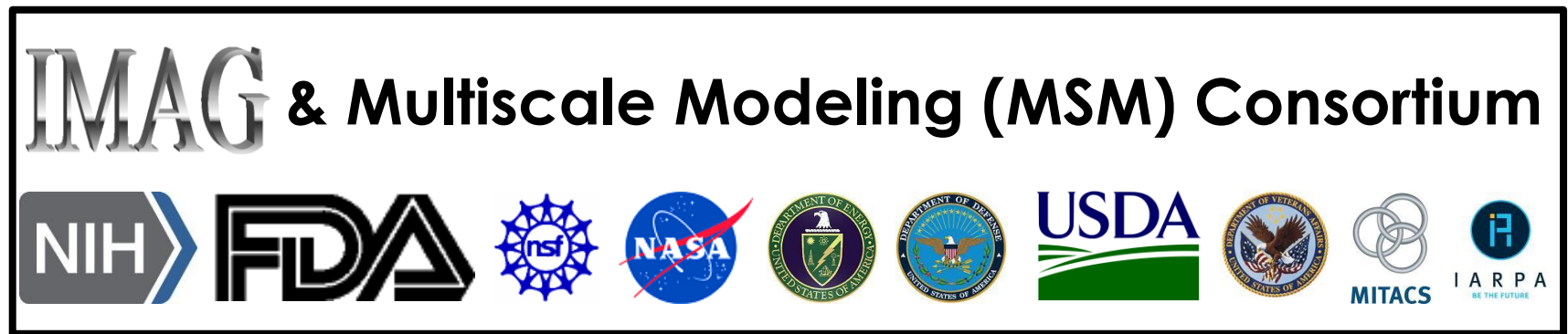
SOLUTION PATHWAY

To bridge this gap, the

Committee on Credible Practice of Modeling & Simulation in Healthcare



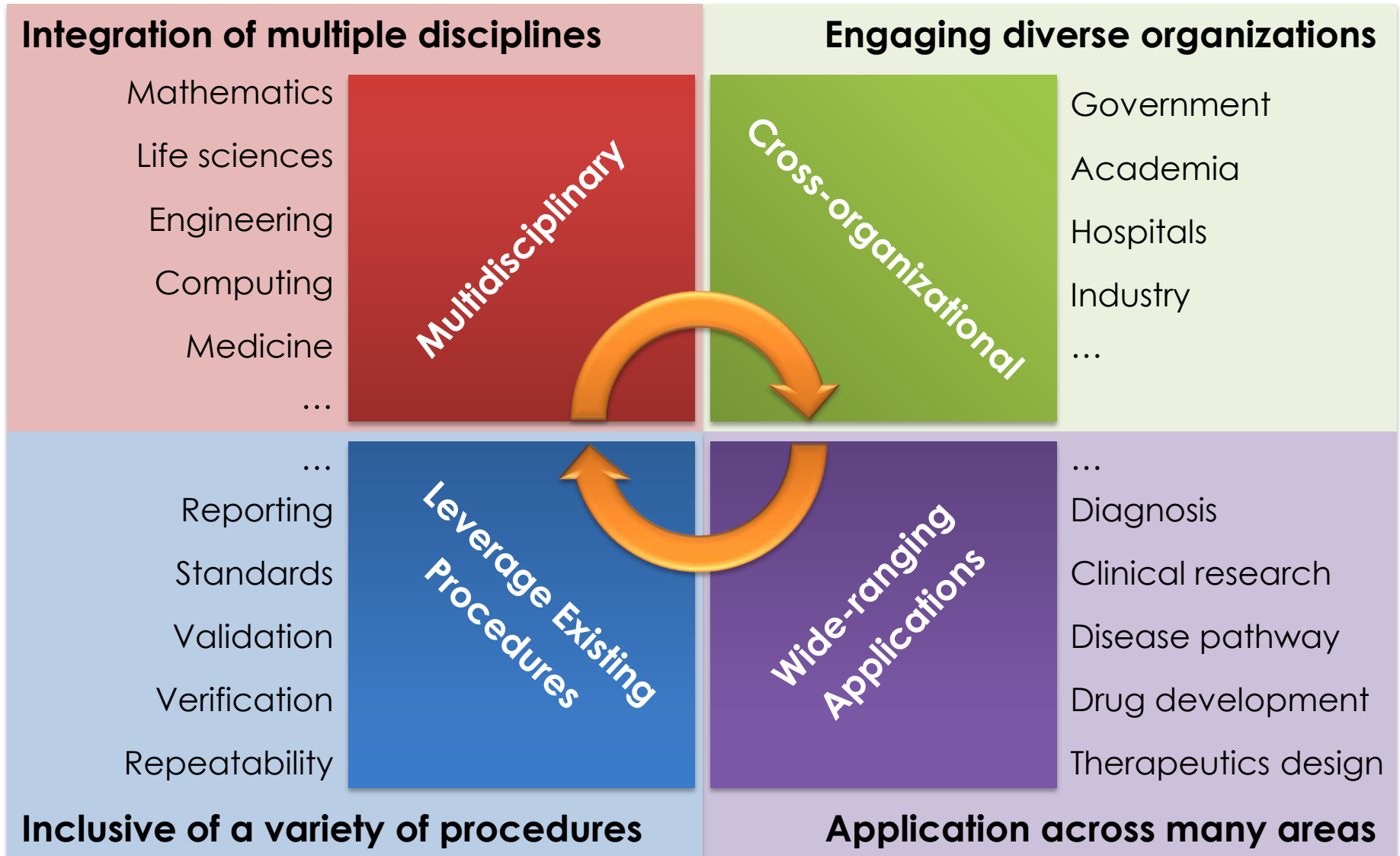
was established under



Primary focus: Computational M&S for clinical research and decision-making



WHAT MAKES THE COMMITTEE UNIQUE?



COMMITTEE IMPLEMENTATION STRATEGY

COMMITTEE EXECUTIVE MEMBERS (EXECUTE & CHARGE)



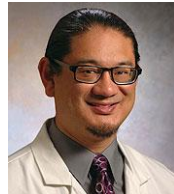
A. Erdemir, Ph.D.
Co-Chair
Cleveland Clinic



L. Mulugeta, M.Sc.
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InSilico Labs, LLC



W. Lytton, M.D.
Kings County Hosp.
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G. An, MD
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NASA



L. Tian, Ph.D.
Stanford U.



T. Morrison, Ph.D.
FDA



J. Ku, Ph.D.
Stanford U.



M. Horner, Ph.D.
ANSYS, Inc.

COMMUNICATION ↔ ACCOUNTABILITY

ADVISORY COUNCIL (REVIEW & ADVISE)



Al. Marsden, Ph.D.
Stanford U.



J. Bischoff, Ph.D.
Zimmer



G. Peng, Ph.D.
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Wyle

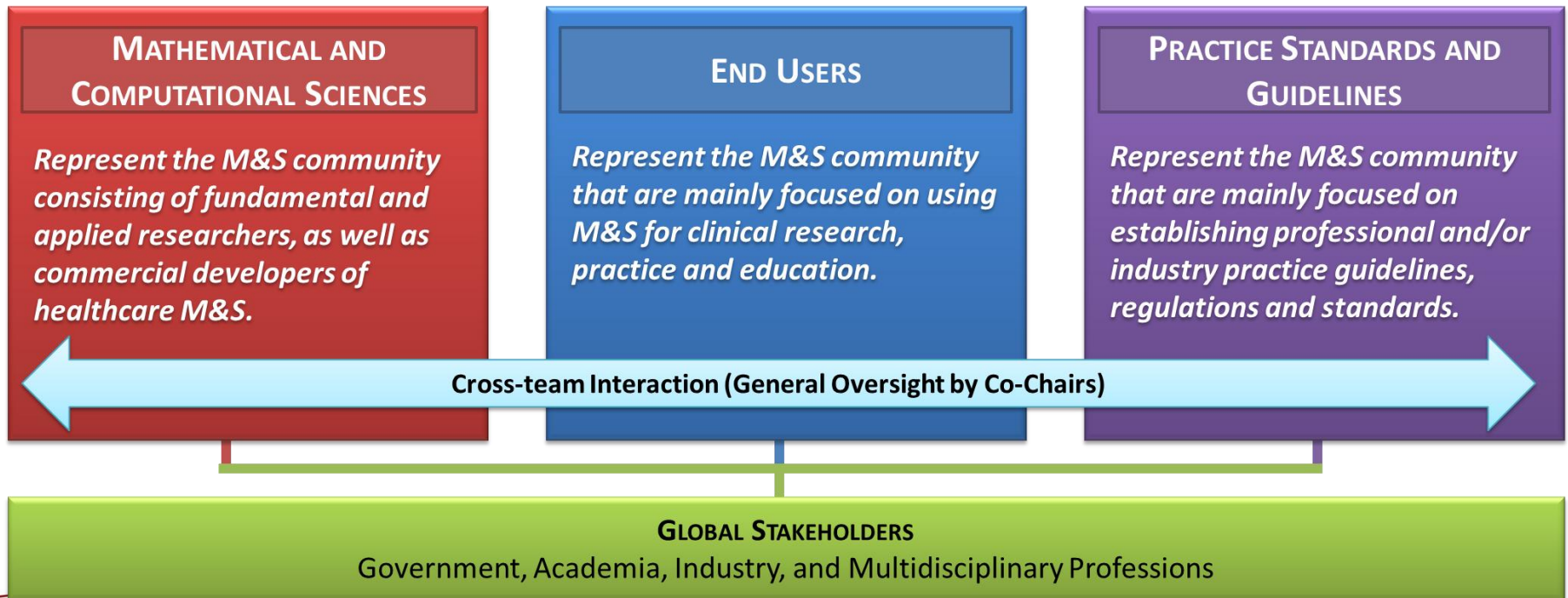
Interagency Modeling and Analysis Group (**IMAG**) & Multiscale Modeling Consortium (**MSM**)

For full credentials of the CPMS members: http://wiki.simtk.org/cpms/CPMS_Members

COMMITTEE IMPLEMENTATION STRATEGY

Use team-based structure 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



COMMITTEE'S CHARGE

- **Guidelines & Procedures**
 - Credible practice in computational medicine
 - Leveraging readily available techniques
 - Define novel translational workflows to enhance credibility practice
- **Demonstrate Workflows**
 - Conduct studies to develop novel credibility assessment procedures
 - Disseminating examples of credibility assessment
- **Consistent Terminology**
 - Unify the use of M&S vocabulary across all stakeholders
- **Promote Good Practice**
 - Bridge synergistic activities within the M&S communities
 - Conduct outreach activities
- **End Products**
 - 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

TEN SIMPLE RULES OF CREDIBLE PRACTICE

Primary deliverable: *“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.

Full details of this activity is available at:

<http://wiki.simtk.org/cpms/Ten Simple Rules of Credible Practice>



INITIAL SURVEY TO IDENTIFY THE “TEN SIMPLE RULES”

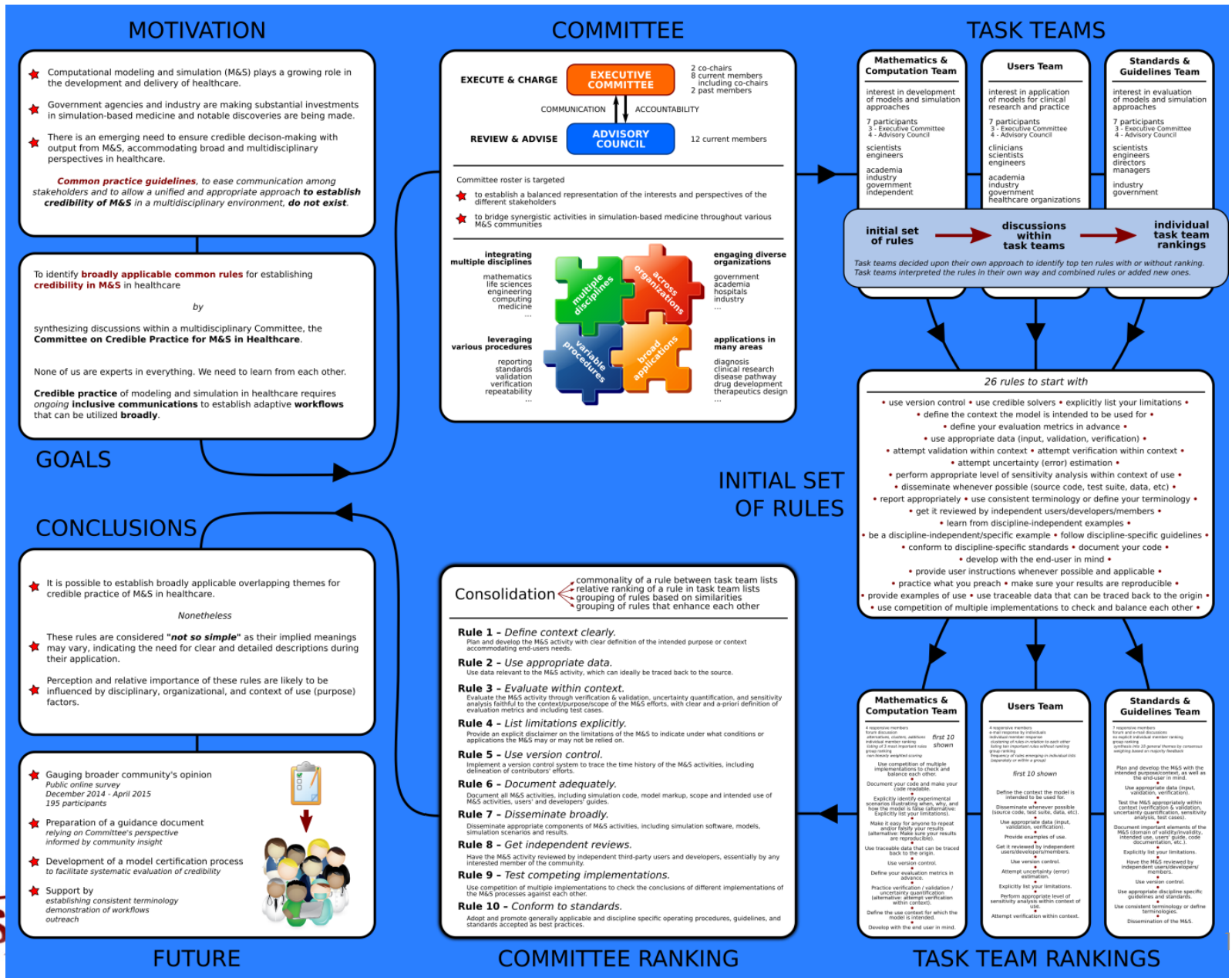
To initiate the Ten Simple Rules task:

1. 26 candidate rules were generated
2. Candidate rules were surveyed internally among the Committee's three Task Teams
3. Results from the three teams were consolidated to arrive at “Ten Simple Rules”

26 Candidate Rules of Credible Practice

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

COMMITTEE'S PERSPECTIVE ON TSR OF CREDIBLE PRACTICE



STATUS OF THE TEN SIMPLE RULES (TSR) ACTIVITY

- In an effort to draw out globally well-balanced guidelines across the range of disciplines and application interests, a public survey was launched on August 15th, 2014 to obtain input from the broader M&S stakeholder community.
- The survey was closed on April 15, 2015 and the Data Analysis Team has started to analyze the results.
- A forum discussion thread has been initiated:
<https://simtk.org/forums/viewtopic.php?f=848&t=5616&sid=fdcab3f040d5c52b8667a0b0812d2e2b>
- The raw data is also available at:
[https://simtk.org/websvn/wsvn/cpms/dat/Survey/Complete%20Survey%20Results Clean 04242015.xlsx](https://simtk.org/websvn/wsvn/cpms/dat/Survey/Complete%20Survey%20Results%20Clean%2004242015.xlsx)

PUBLICLY SURVEYED PROPOSED RULES

1	Engage potential end-user base.	19	Learn from specialized and broadly applicable guidelines for good practice.
2	Make the M&S results reproducible.	20	Follow discipline-specific guidelines and standards whenever possible.
3	Develop the M&S with the end-user in mind.	21	Perform uncertainty estimation/quantification within context of use.
4	Use appropriate data, e.g., for input, validation, verification.	22	Perform numerical error estimation/quantification within context of use.
5	Explicitly identify experimental scenarios that illustrate when, why, and how the M&S is false or not applicable.	23	Get the M&S reviewed by independent users, developers, and members of the intended stakeholder community.
6	Use competition of multiple M&S implementation methods to check and balance each other.	24	Explicitly list limitations of the M&S.
7	Document the development and use of M&S appropriately.	25	Make it easy for anyone to repeat and/or falsify your results.
9	Use version control, i.e., to track different revisions of the model.	26	Use consistent terminology or define your terminology.
10	Be a discipline specific example of good practice.	27	Verify the M&S processes within context of use.
11	Use data that can be traced back to the origin of source.	28	Report appropriately, i.e., to allow reproducibility, to assess reliability, and to establish accountability.
12	Disseminate whenever and whatever is possible, e.g., source code, test suite, data.	29	Define the context in which the M&S is intended to be used.
13	Validate the M&S activity within the context of use.	30	Use credible, e.g. verified, solvers (code, software, applications).
14	Perform sensitivity analysis within the context of use.	31	Conform to discipline-specific standards.
15	Define the M&S evaluation metrics in advance.	32	Disclose conflict of interests.
16	Make your code readable.	33	Adopt and promote standard operating procedures.
17	Provide user instructions whenever possible and applicable.	34	Document your code.
18	Provide examples of use.	35	Provide clear descriptions of limitations.
		36	Use simulation software with established reliability.

CURRENT STATUS OF SURVEY ANALYSIS

0	1	2	3	4	5
Not Applicable Not Important	Low Importance	Moderately Important	Important	Very Important	Extremely Important

- Total responses: 186
- Total valid responses: 148 from
 - 4 continents, 10 disciplines, various levels of education and experience in M&S

Key Overlaps between Committee's perspectives & global M&S community

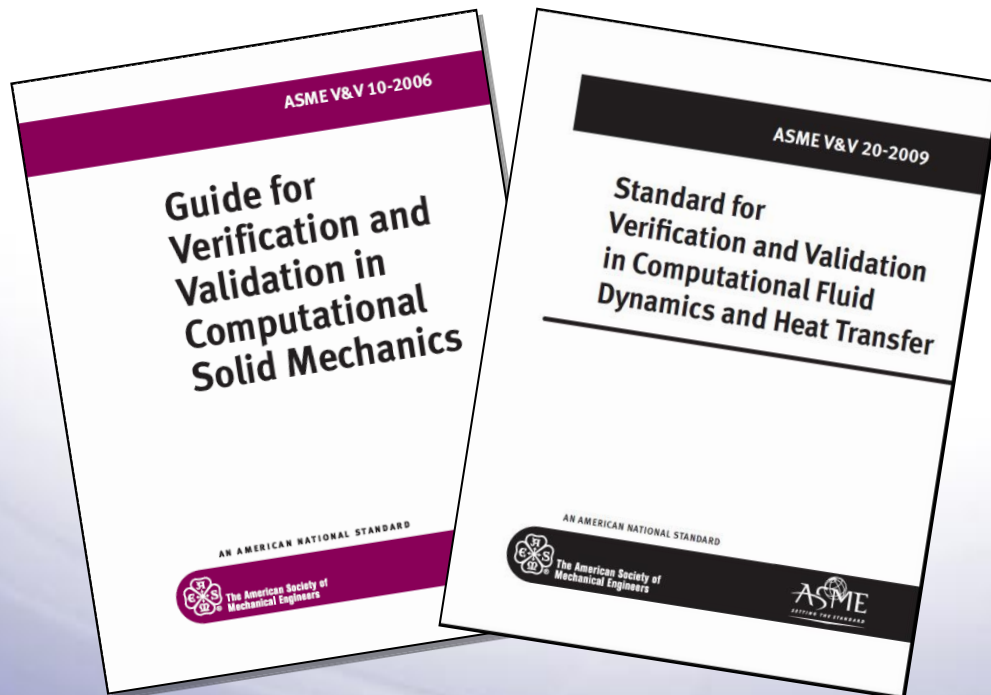
Simple Rule	Description
Define context clearly	Develop and document the subject, purpose, and intended use(s) of the model or simulation
Use appropriate data	Employ relevant and traceable information in the development or operation of a model or simulation.
Evaluate within context	Verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation are accomplished with respect to the reality of interest and intended use(s) of the model or simulation.
List limitations explicitly	Restrictions, constraints, or qualifications for or on the use of the model or simulation are available for consideration by the users or customers of a model or simulation.

FUTURE WORK

- Publish Committee's perspective, *'Ten "Not So" Simple Rules for Credible Practice of Modeling and Simulation in Healthcare: Perspectives from a Multidisciplinary Committee'*
- Analyze public survey data, and publish results in PLOS Computational Biology in the form of *"Ten Simple Rules of Credible Practice of M&S in Healthcare"*
- Develop and publish the *"Guidelines for Credible Practice in Modeling & Simulation in Healthcare"* and as well as a *"Model Certification Guideline"* based off of the above findings
- Publish glossary of terms to help unify the use of M&S terminology across a variety of disciplines and stakeholders in the field – Draft: <http://tinyurl.com/ze4scnx>

ASME Committee on V&V in Computational Modeling and Simulation

- Standards Committee
 - Provide procedures for assessing and quantifying the accuracy and credibility of computational modeling and simulation



V&V Standards Committee in Computational Modeling and Simulation

V&V 10 - Verification and Validation in Computational Solid Mechanics

V&V 20 - Verification and Validation in Computational Fluid Dynamics and Heat Transfer

V&V 30 - Verification and Validation in Computational Simulation of Nuclear System Thermal Fluids Behavior

V&V 40 - Verification and Validation in Computational Modeling of Medical Devices

V&V 50 - Verification and Validation of Computational Modeling for Advanced Manufacturing

- ASME V&V 40 Charter
 - Provide procedures to standardize verification and validation for computational modeling of medical devices
 - Charter approved in January 2011
- Motivating factors
 - Regulated industry with limited ability to validate clinically
 - Increased emphasis on modeling to support device safety and/or efficacy
 - Use of modeling hindered by lack of V&V guidance and expectations within medical device community

V&V Standards Committee in Computational Modeling and Simulation

V&V 10 - Verification and Validation in Computational Solid Mechanics

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V&V 30 - Verification and Validation in Computational Simulation of Nuclear System Thermal Fluids Behavior

V&V 40 - Verification and Validation in Computational Modeling of Medical Devices

V&V 50 - Verification and Validation of Computational Modeling for Advanced Manufacturing

V&V 40 Subcommittee Membership

Carl Popelar, Chair, Southwest Research Institute

Tina Morrison, Vice-Chair*, FDA

Andrew Rau, Vice-Chair, Exponent

Ryan Crane, Secretary, ASME

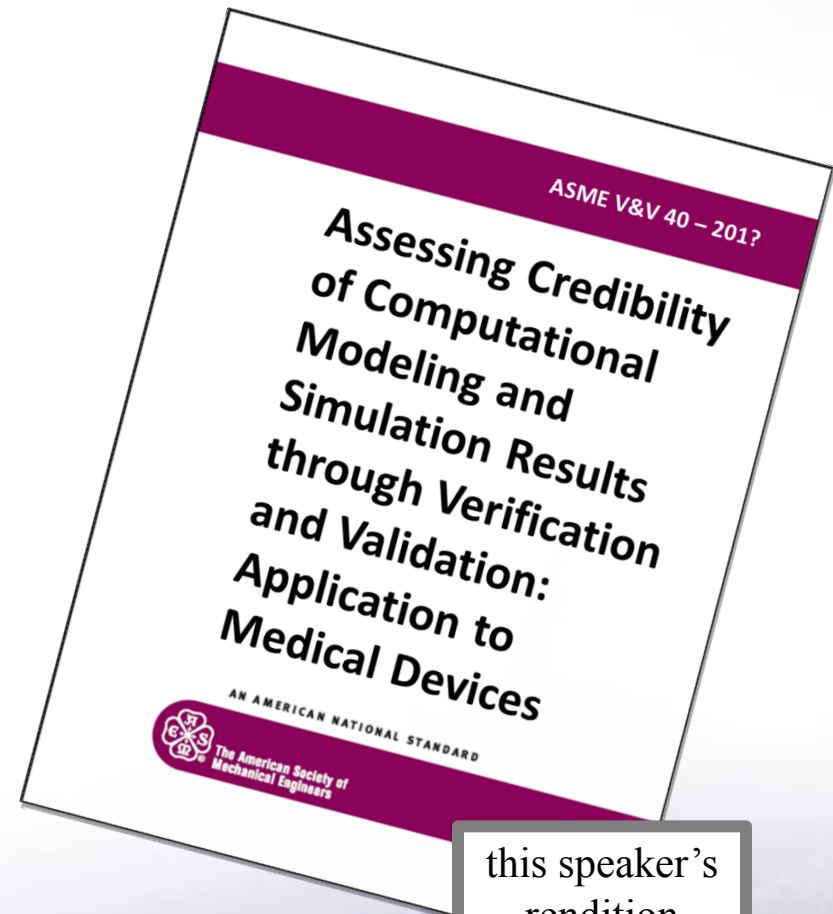
P. Afshari, Depuy-Synthes Spine
B. P. Baillargeon, Dassault Systemes Simulia Corp
D. Bardot, Medical Device Innovation Consortium
A. Bestelmeyer, BD Technologies
J. Bischoff, Zimmer
J. P. Bodner, Medtronic Corp
S. Cheng, Integra Life Sciences
B. D. Choules, MED Institute
R. Chow, Consultant
J. C. Coburn, US Food and Drug Administration
C. Corrales, Baxter Healthcare Corporation
K. K. Debus, Cd-adapco
M. Dharia, Zimmer Biomet
S. Eswaran, Abbott Vascular
C. Funkhouser, Baxter Healthcare Corporation
K. Genc, Simpleware Inc.
M. Goodin, Simutech Group
I. Guler, Boston Scientific Corporation
A. Gupta, Google Inc.
P. Hariharan, US Food and Drug Administration
W. Hary, Heartflow

M. Horner, ANSYS, Inc.*
H. Jin, Medtronic, Inc.
A. Kiapour, 4WEB Medical Inc.
L. Knudsen, Synchroness
S. Kulkarni, VEXTEC Corporation
D. Levine, Zimmer, Inc.
X.M. Li, Consultant
X Liu, Stryker Orthopaedics
B. A. Lurie, W.L. Gore
R. Marinescu, Smith & Nephew
J. Mast, Hill-Rom, Inc.
L. Mulugeta, Independent
W. A. Olson, Ethicon Endo-surgery
T. L. Rossman, Mayo Clinic
P. Saffari, Endologix
C. Scotti, W.L. Gore
R. Swift, Cook Research Inc.
P. Tomaszewski, Depuy Orthopaedics Inc
T. Zhao, Edwards Lifesciences
A. U. Nair, *Alternate*, BD Technologies
N. R. Rebelo, *Alternate*, SIMULIA Western Region

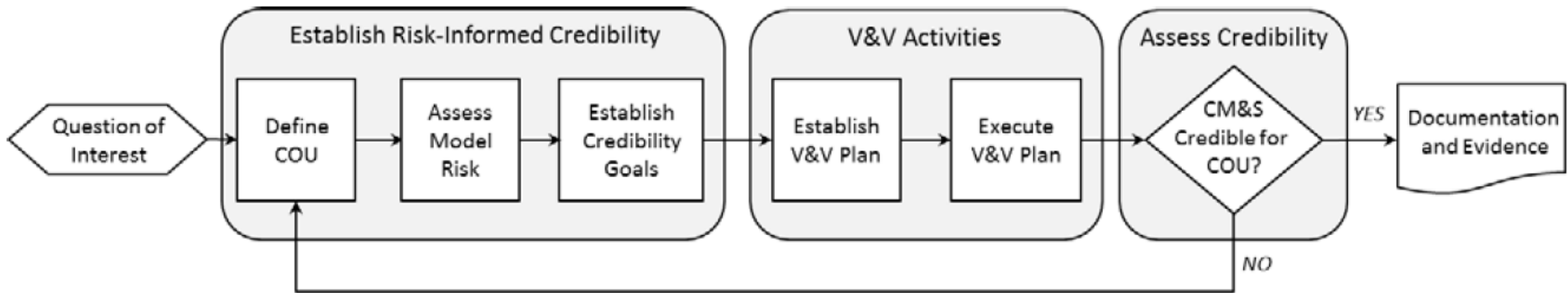
* *Standards Committee representative*

V&V 40 Activities

- Current effort focused on completing a standard or guide:
 - Document recently completed 2nd round of sub-committee balloting.
 - Comments were primarily editorial in nature with a few technical issues to be addressed.

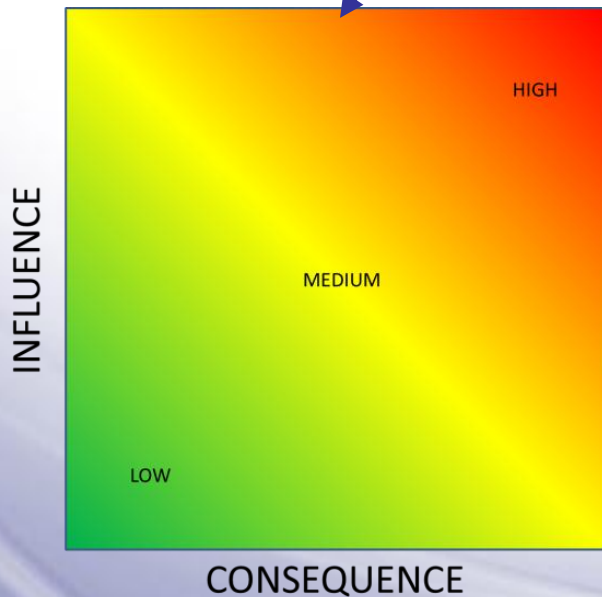
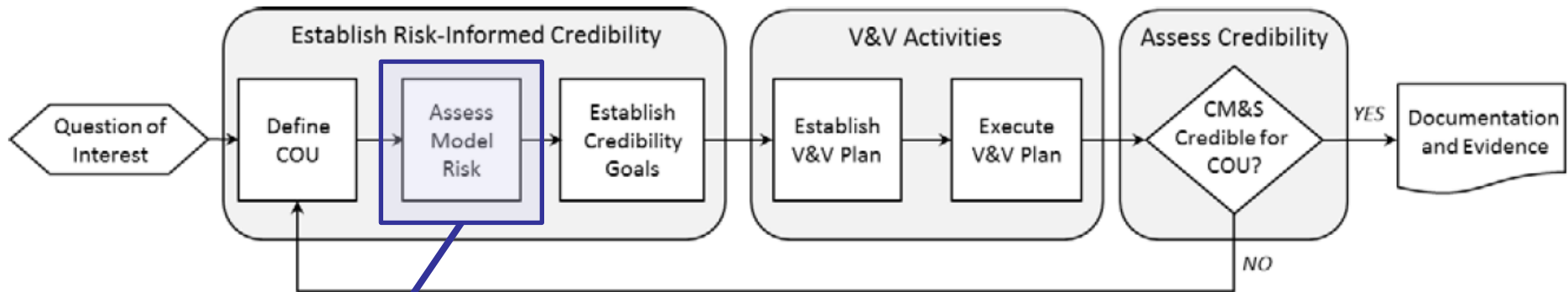


Risk-Informed Credibility Assessment Method



The V&V40 guide outlines a process for making risk-informed determinations as to whether CM&S is credible for decision-making for a specified context of use.

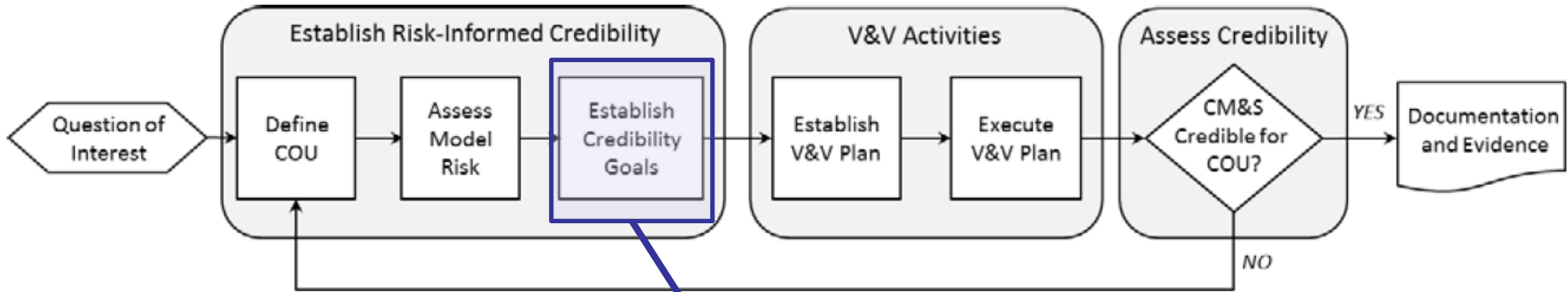
Risk Assessment



CM&S influence is the contribution of the CM&S to the decision relative to other available evidence.

Decision consequence is the significance of an adverse outcome resulting from an incorrect decision.

Credibility Assessment



Model credibility refers to the trust in the predictive capability of the computational model for the COU.

Trust can be established through the collection of V&V evidence and by demonstrating the applicability of the V&V activities to support the use of the CM for the COU.

Credibility Factors														
Verification				Validation						Applicability				
Code		Solution		Model			Comparator			Output Assessment		Applicability		
Software Quality Assurance	Numerical Algorithm Verification	Discretization Error	Use Error	Numerical Solver Error	System Configuration	System Properties	Boundary Conditions	Governing Equations	Sample Characterization	Control Over Test Conditions	Measurement Uncertainty	Equivalency of input and output types	Rigor of Output Comparison	Relevance of the Quantities of Interest

Examples

Example 2: Context of Use

Medical device: a new posterior stabilized total knee arthroplasty assembly

Context of Use: Finite element analysis (FEA) will be used to determine if the locking mechanism has sufficient strength to prevent lift-off of the new device. Specifically, the model predicts the QOI of liftoff of the tibial component under a variety of loads. The tibial component liftoff is evaluated exclusively using the computational model. All device configurations will be simulated. No predicate device exists to compare with the computed results. No benchmark device exists for a particular device. However, these FEA techniques have been

Example 3: Model risk

Medical device: centrifugal blood pump for circulatory support

Context of Use: Use computational fluid dynamics identify the key pump features whose dimensional variation could potentially lead to increased hemolysis; those features will be directly assessed with testing. Results will be compared against a predicate device.

CM&S influence: based on the classification scheme below, the model influence is medium because testing will be used to confirm some of the results.

Example 4: Rigor of Output Comparison

Medical device: centrifugal blood pump for circulatory support

From Example 3, model risk was determined to be Medium-High. This result is directly used to determine the validation assessment criteria for "Rigor of Output Comparison":

Within the scheme presented, the assessment levels for CM&S validation are as follows:

1. Visual comparison concludes good agreement.
2. Comparison by simply measuring the differences between computational results and experimental data. Differences are less than 20%.
3. Comparison by simply measuring the differences between computational results and experimental data. Differences are less than 10%.
4. Comparison with uncertainty captured and incorporated from the comparator or computational model. Differences are less than 5%, including consideration of some uncertainty, but statistical distributions for further uncertainty quantification are unknown.
5. Comparison with uncertainties captured and incorporated from both the comparator and the computational model, including comparison error. Differences are less than 5%, and statistical distributions are known for rigorous treatment of uncertainty.

Based on a Medium-High model risk for the blood pump, the validation activities should Level 4, demonstrating model accuracy to within 5 with uncertainty captured.

direct decision to alter the key pump feature's dimensional tolerances to monitor hemoglobin levels during clinical use if hemolysis occurs. Patient injury may require intervention of the clinician to monitor patient hemoglobin levels. Therefore, the decision consequence is HIGH.

Medium-High. This result is directly used to determine the validation assessment criteria for "Rigor of Output Comparison," see Example 4.

	Consequence		
	Low	Medium	High
Low	1	2	3
Medium	2	3	4
High	3	4	5

COMPARISON SUMMARY

	CPMS	V&V40
Mission Statement	To establish credible practice guidelines, consistent terminology and proposed model certification process, as well as to demonstrate workflows and identify new areas of research for reliable development and application of M&S in healthcare practice and research.	Provide procedures to standardize verification and validation for computational modeling of medical devices.
Primary stakeholders	Computational M&S in healthcare as a whole – mainly driven by research initiatives under the IMAG Multi-scale Modeling Consortium	Biomedical device industry, industry service providers, and regulatory and standards bodies such as the US Food and Drug Administration (FDA) and ASME
End-product(s)	<ol style="list-style-type: none"> 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 	<ol style="list-style-type: none"> I. A standard (or guide) for, “Assessing Credibility of Computational Modeling & Simulation Through Verification & Validation: Application to Medical Devices” II. Series of examples that demonstrate application of one or more components of the standard
Approach to developing end-product(s)	<ul style="list-style-type: none"> • Executive Committee (EC) executes mission • Advisory Council provides guidance to the EC • Extensive use of crowd-sourcing of the healthcare and M&S community through surveys, wiki contributions and forum discussions 	<ul style="list-style-type: none"> • V&V40 sub-committee establishes standard direction through consensus • Sub-groups, working groups, and task groups execute tasks related to governing scientific methods, devices, and content writing.
General credibility workflow	Apply the Ten Simple Rules of Credible Practice with appropriate intensity for given context of use (iterative).	Define Context of Use → Assess Model Risk → Establish Credibility Goals → Establish & Execute V&V Plan (iterative) → Assess Credibility → Document



**Committee on Credible Practice of
Modeling & Simulation in Healthcare**

<https://simtk.org/home/cpms>

QUESTIONS?

Codes & Standards

V&V 40 VERIFICATION AND VALIDATION IN COMPUTATIONAL
MODELING OF MEDICAL DEVICES

<https://cstools.asme.org/csconnect/CommitteePages.cfm?Committee=100108782>

ASME 2016 V&V Symposium

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)*

Credible Practice of Modeling & Simulation in Healthcare

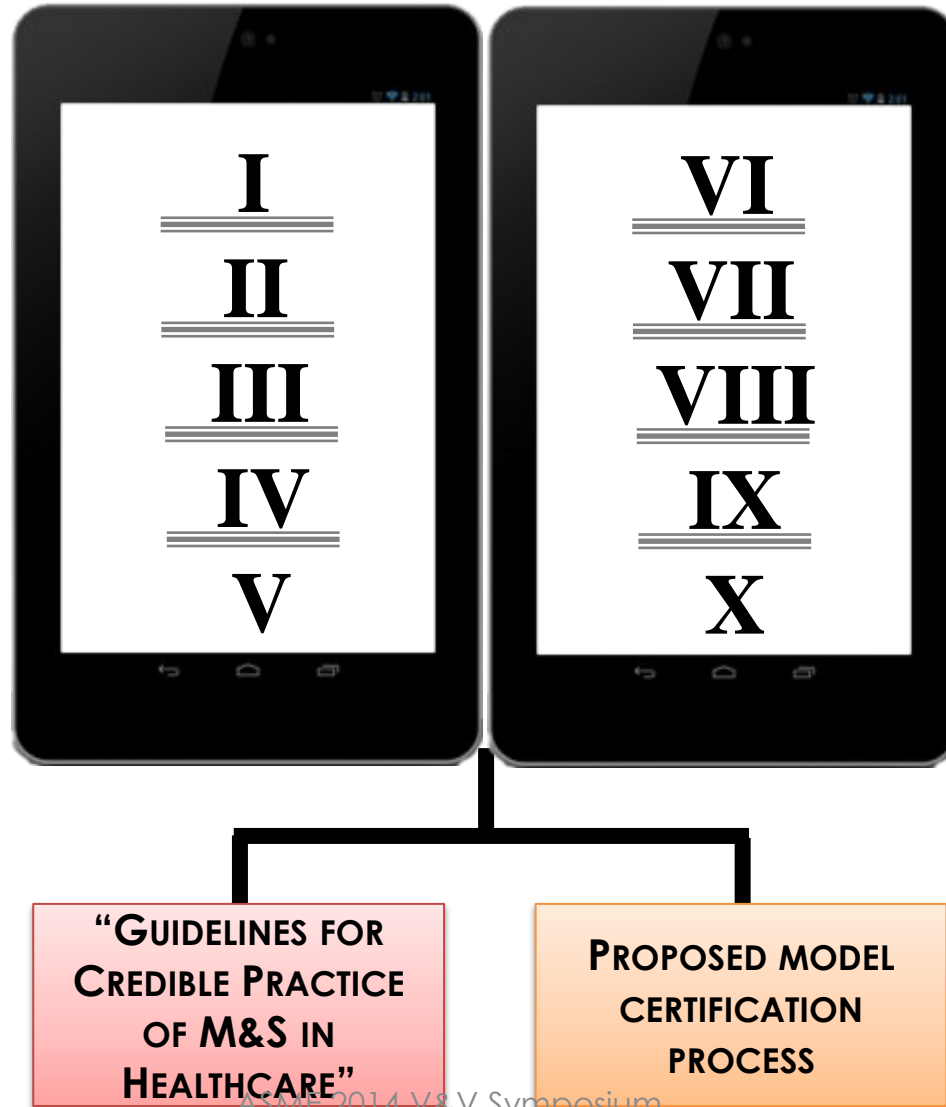
computational solution of models to quantify descriptive and predictive metrics of system(s) of interest; including related post-processing efforts to calculate these metrics from raw analysis results

Credible Practice of Modeling & Simulation in Healthcare

*any activity involving **development, maintenance, advancement, or administration of medical care;** including research, diagnosis, risk assessment, prevention, therapy, rehabilitation, surgery, intervention design, and regulation*

UPCOMING: TEN SIMPLE RULES, GUIDELINES & CERT.

COMMUNITY GENERATED TEN SIMPLE RULES



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



Example

Simtk Wiki - cpms [Glossary and Definitions/ credibility](#)

FrontPage | RecentChanges | FindPage | HelpContents | **credibility**

Immutable Page | Info | Attachments | More Actions: ▾

Overview

Team

Downloads

Documents

Wiki

Publications

News

Public Forums

Advanced

Downloads & Source Code

This project has no public downloads, but makes [source code](#) available.

Credibility

Dictionary Definition

Needs contribution

Committee Definition

Needs contribution

Domain Specific Usage

Engineering and Biomedical (NASA): The quality to elicit belief or trust in M&S results. ¹

Notes

¹ from NASA STANDARD FOR MODELS AND SIMULATIONS – <https://standards.nasa.gov/documents/detail/3315599>.

ASME 2014 V&V Symposium

GOAL: ADOPTION OF GUIDELINES BY STAKEHOLDERS

Goal Oriented Activity: Active engagement of the global stakeholder community to ensure that the guidelines established capture the primary interests of the computational medicine community, and are widely adopted

Open discussions and contribution to activities:

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

URL: <https://simtk.org/home/cpms>



Overview
Statistics
Geography of use

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Downloads & Source Code

Credible Practice of Modeling & Simulation in Healthcare

Project Overview

Description: This project houses the activities of the Committee on Credible Practice of Modeling & Simulation in Healthcare. This is an initiative started at the Interagency Modeling and Analysis Group and Multiscale Modeling Consortium (<http://www.imagwiki.nibib.nih.gov>). Tentative charges of the Committee are to:

- adopt a consistent modeling & simulation terminology,
- define accreditation procedures for modeling and simulation practice,
- demonstrate accreditation workflows, and

Project Lead

Ahmet Erdemir
Contact

Lealem Mulugeta
Contact

CPMS