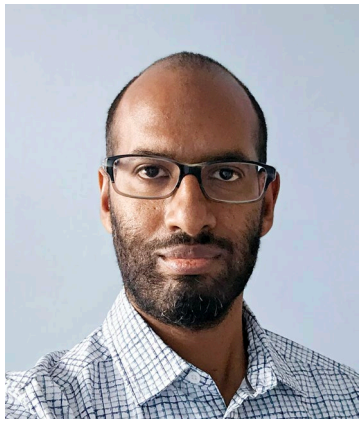
Assessing the credibility of computational modeling and simulation for medical devices: Final FDA Guidance

Pras Pathmanathan, PhD
Division of Biomedical Physics
Office of Science and Engineering Laboratories (OSEL)
Center for Devices and Radiological Health (CDRH)
FDA

Acknowledgements

Kenneth Aycock
OSEL/DAM
Kenneth.Aycock@fda.hhs.gov

Brent Craven
OSEL/DAM
Brent.Craven@fda.hhs.gov



Pras Pathmanathan
OSEL/DBP
Pras.Pathmanathan@fda.hhs.gov

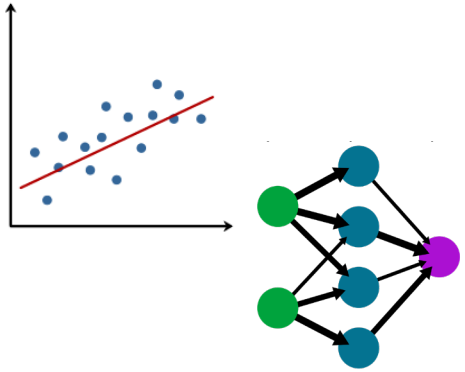
What is computational modeling and simulation (CM&S)?

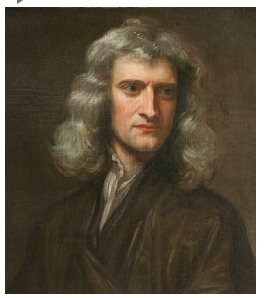
Data-driven models
- Statistical methods, e.g., regression
- Machine learning and AI

Hybrid methods
- First-principles model with data-driven sub-model(s)
- Train ML model to first-principles model results
- Physics-informed neural networks

First-principles models
- Physics-based models
- Mechanistic models

Mathematical models





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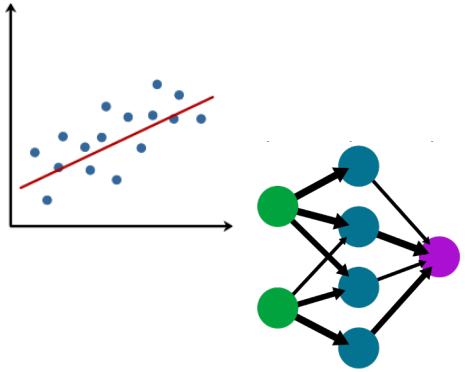
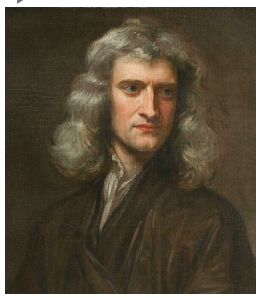
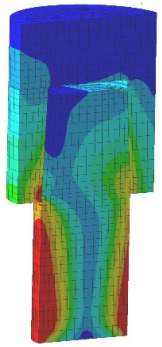




CM&S in regulatory submissions

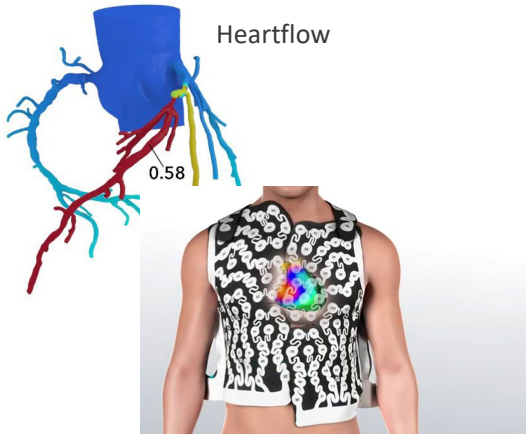
In Silico Device Testing

Simulate device to generate safety/ effectiveness evidence



CM&S in device software

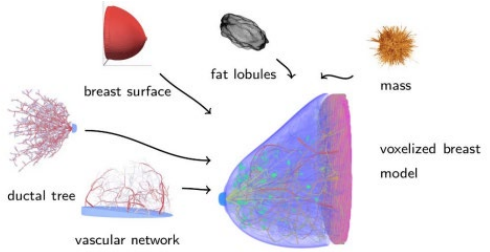
Algorithm in device software takes in patient data and simulates the patient



CardioInsight

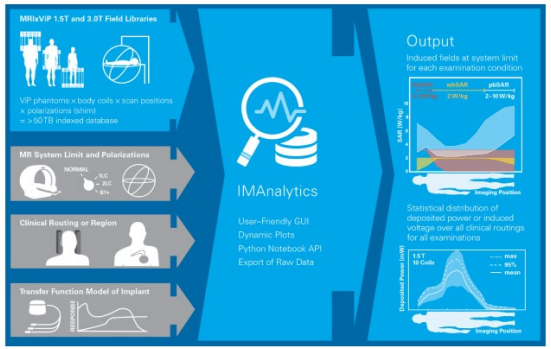
In Silico Clinical Trial

Device performance is evaluated using a 'virtual cohort' of simulated patients.



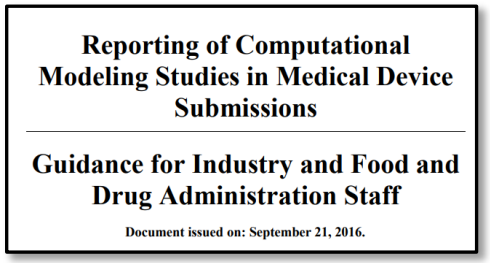
OSEL VICTRE project

CM&S-based MDDT



IMAnalytics

Timeline



CDRH M&S Reporting Guidance

OSEL Credibility of Models Regulatory Science Program

~2010

Growing awareness in devices community (incl. CDRH) of need for standardized credibility assessment

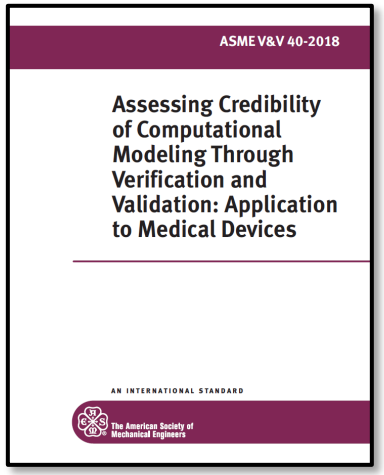
2013

ASME V&V40 subcommittee formed

2016

2018

ASME V&V40 Standard



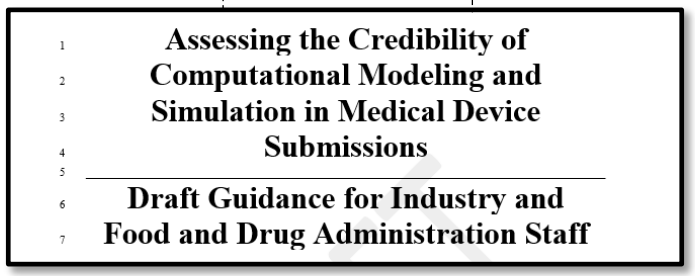
2020

2021

Draft Guidance

2023

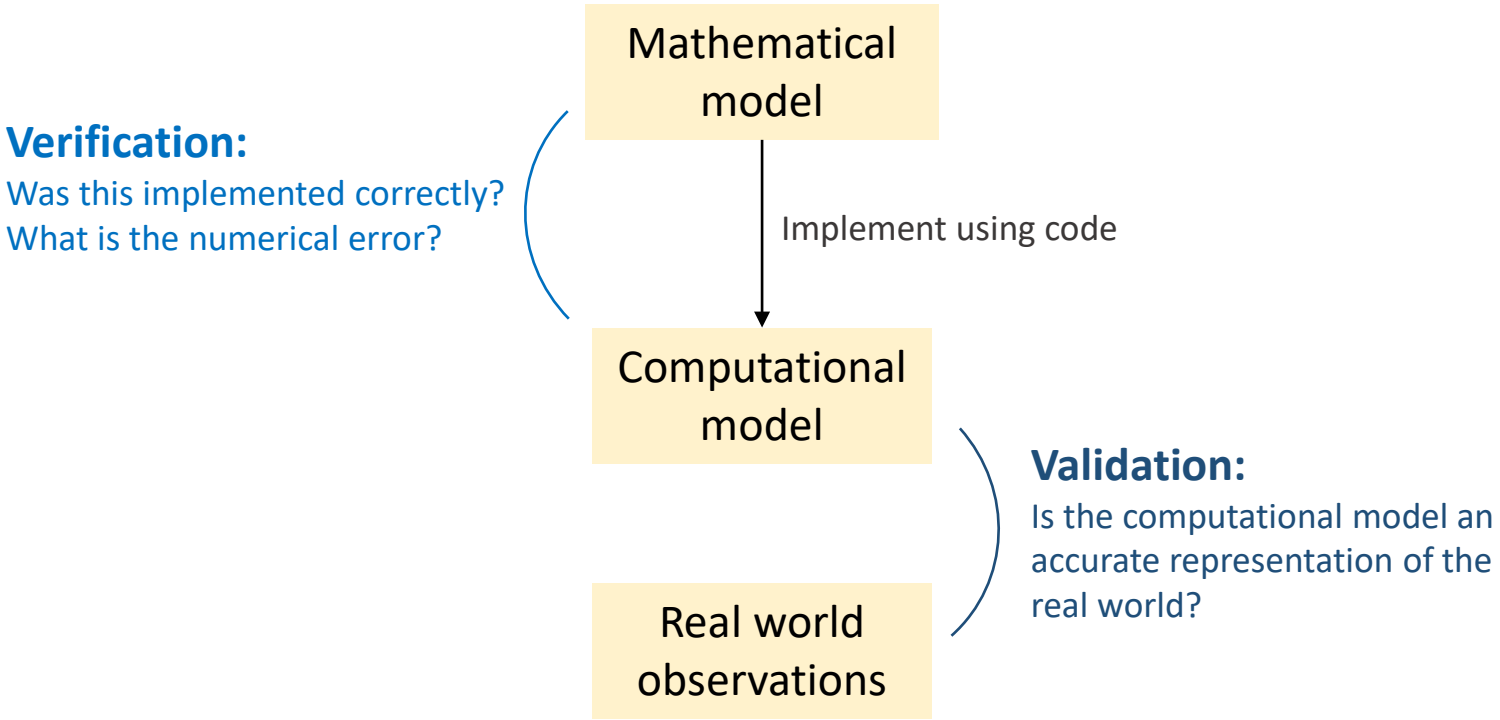
Final Guidance



Key Definitions

Paraphrased from Credibility Guidance, originally from ASME V&V40 2018:

- **Credibility** – "the trust, based on all available evidence, on the predictive capability of a computational model"
- **Context of use (COU)** – "the role and scope of the computational model in answering the question of interest"



Scope of the guidance

In scope

- First principles-based models
- For hybrid models:
  - First-principles model components

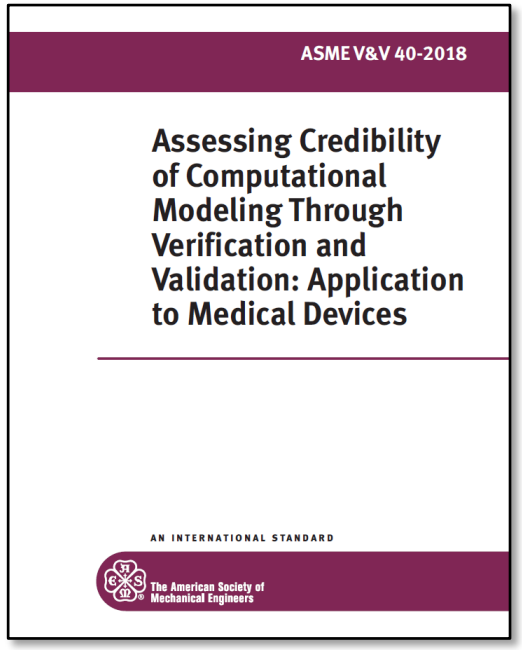
Out of scope models

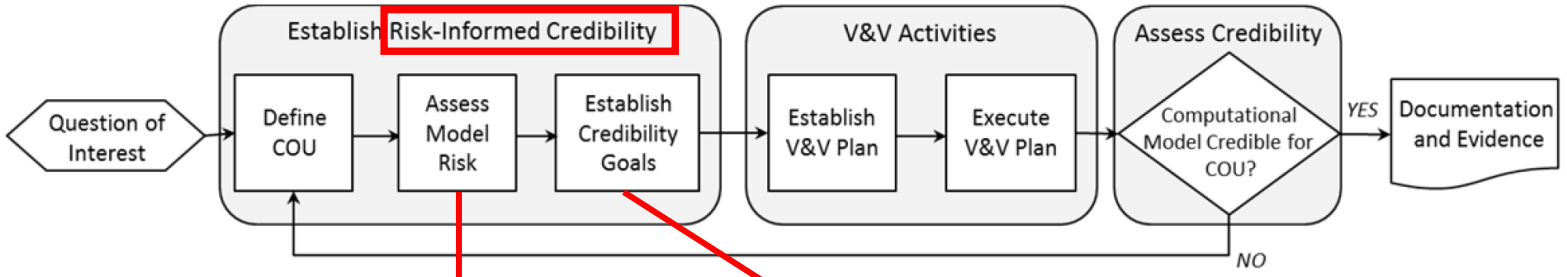
- Standalone statistical or data-driven models
- Models with no simulation, e.g., anatomical models

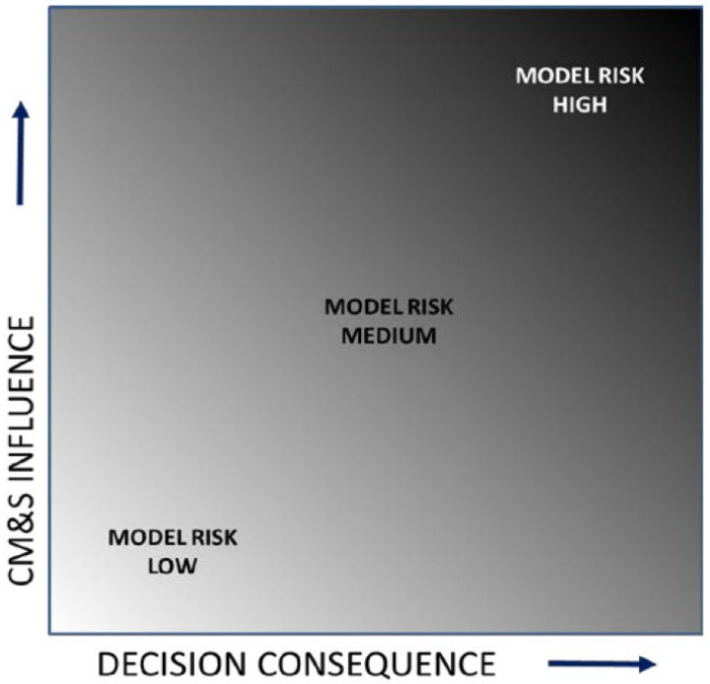
Also out of scope

- How to perform modeling studies
- Technical details for how to perform credibility assessment
- Specific level of credibility needed for regulatory submissions

ASME V&V40 2018







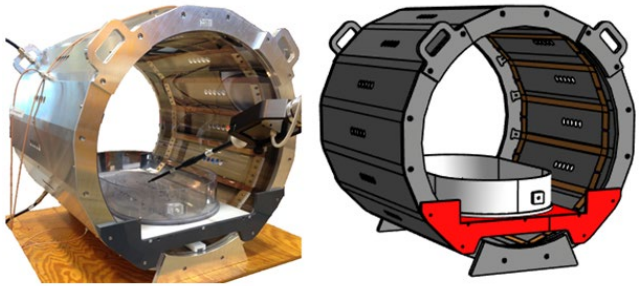
Activities		Credibility Factors
Verification	Code	Software Quality Assurance
		Numerical Code Verification
	Calculation	Discretization Error
		Numerical Solver Error
		Use Error
Validation	Computational Model	Model Form
		Model Input
	Comparator	Test Samples
		Test Conditions
	Assessment	Equivalency of Input Parameters
		Output Comparison
Applicability		Relevance of the Quantities of Interest
		Relevance of the Validation Activities to the COU

Guidance – key points and approach

- Consistent with ASME V&V40-2018
  - **Risk-informed** credibility assessment
  - Can follow Guidance by following V&V40
  - Emphasis on **question of interest, context of use** and **model risk**

- Provides a general framework for model credibility assessment
  - Intended to be applicable to **all** CM&S models, applications and types of regulatory submission
  - **Not prescriptive**

- Framework extends approach of ASME V&V40 2018
  - ASME V&V40 implicitly assumes validation against prospective well-controlled bench tests



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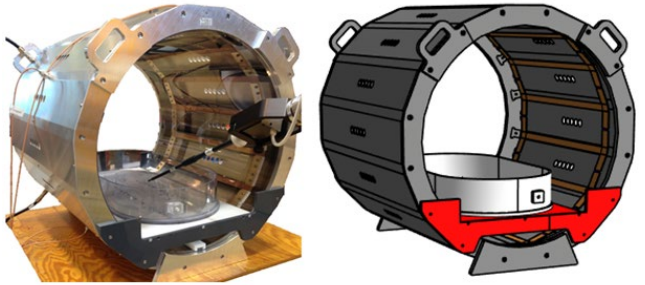

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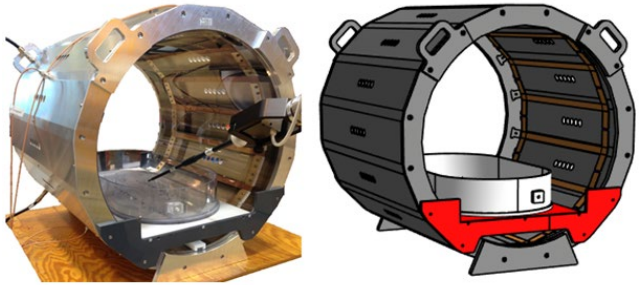
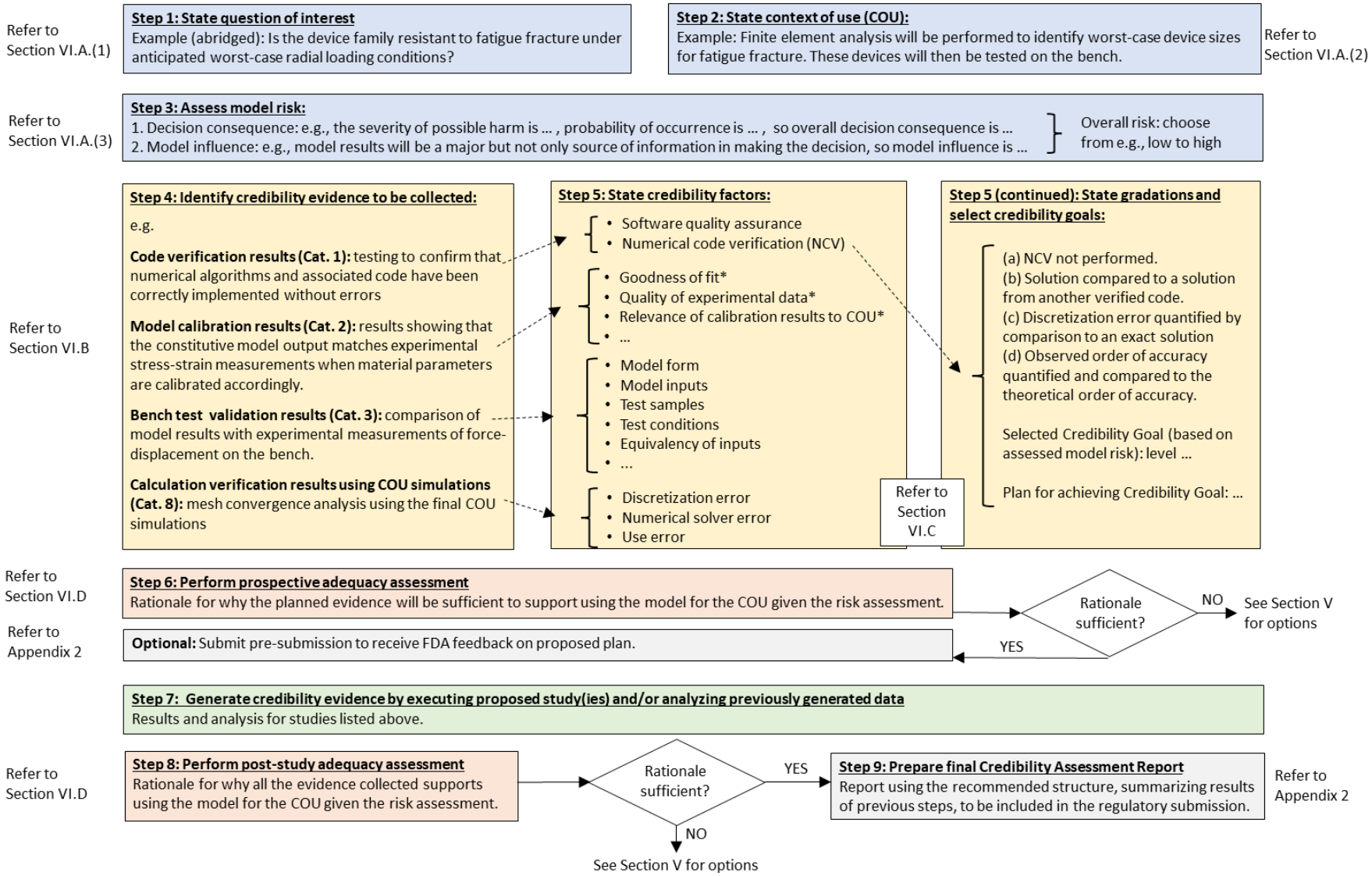


Framework

Guidance Figure 1:



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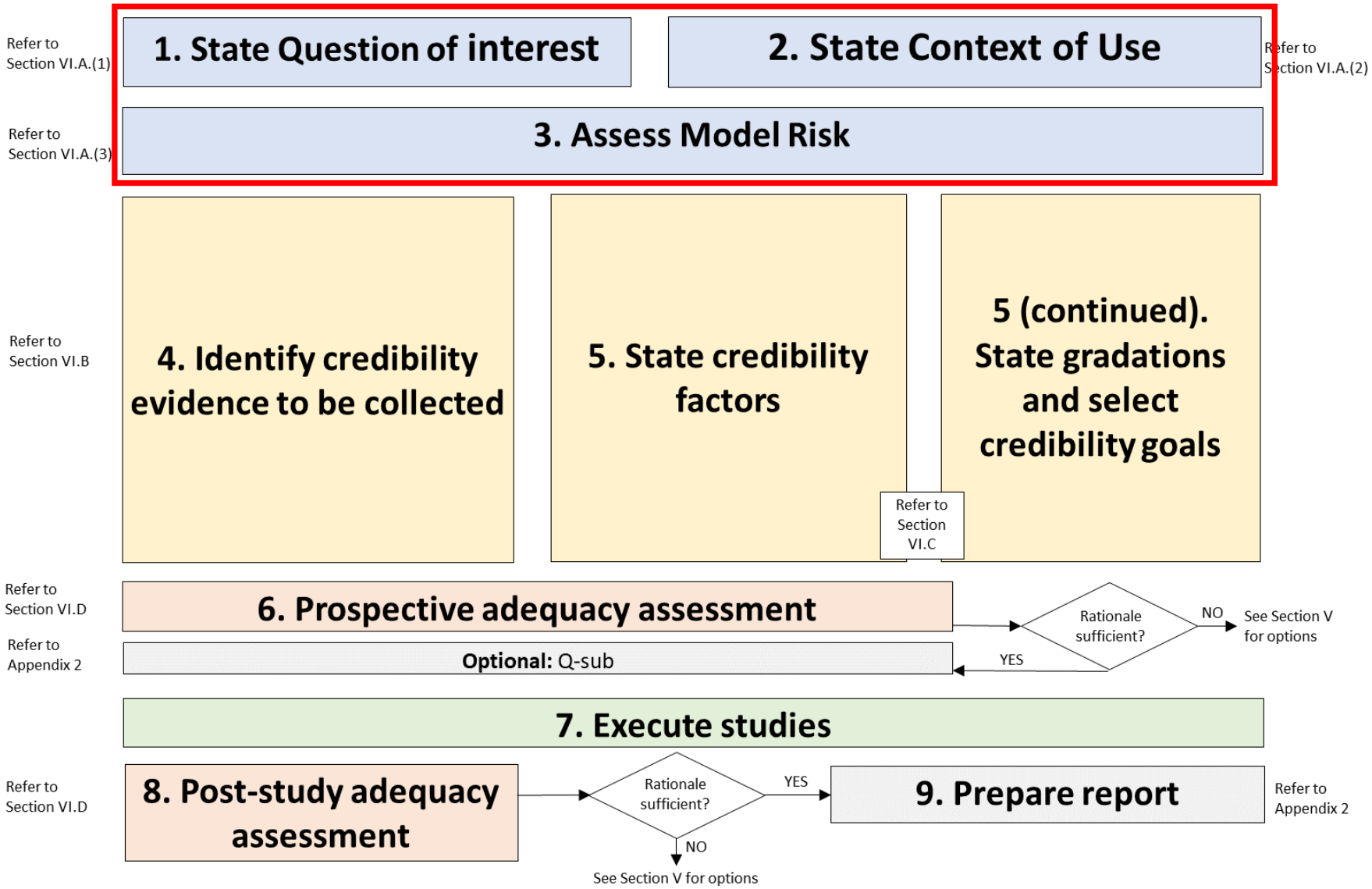
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5. State credibility factors
Refer to Section VI.C
5 (continued). State gradations and select credibility goals
Refer to Section VI.D
6. Prospective adequacy assessment
Rationale sufficient?
NO
See Section V for options
YES
Refer to Appendix 2
Optional: Q-sub
7. Execute studies
Refer to Section VI.D
8. Post-study adequacy assessment
Rationale sufficient?
YES
9. Prepare report
Refer to Appendix 2
NO
See Section V for options

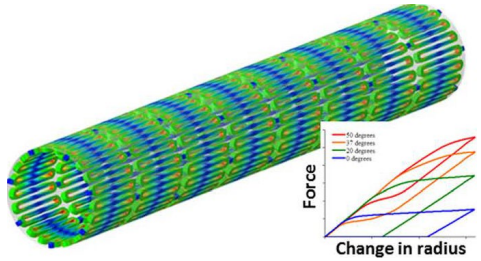
Step 1: state the **Question of Interest**

"the specific question, decision, or concern that is being addressed"

- Should be about the real world
- Not about the model
- Should not be overly broad (i.e., not "Is the device safe?")

Device testing example

Is the device resistant to fatigue fracture under anticipated worst-case radial loading conditions?



Step 2: state the **Context of Use**

"the role and scope of the computational model in answering the question of interest"

- what is modeled and how model outputs used to answer the question of interest
- type of modeling, key inputs and outputs
- whether other information (e.g., bench/animal/clinical) will be used to answer the question of interest

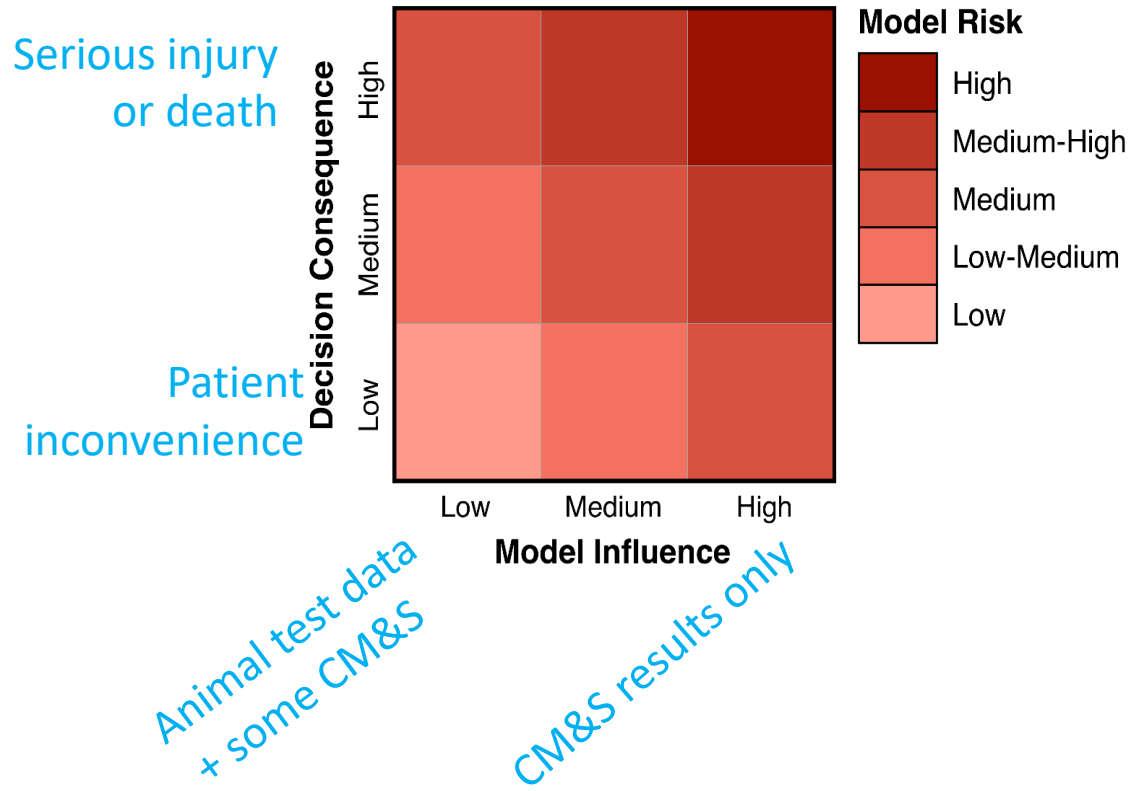
Device testing example
Combine computational modeling predictions and empirical fatigue testing observations to estimate device fatigue safety factors under anticipated worst-case radial loading conditions […]

Step 3: assess **Model Risk**

> "the possibility that the computational model and the simulation results may lead to an incorrect decision that would lead to an adverse outcome"

- Broken down into **model influence** and **decision consequence**

- Decision consequence
  - significance of an adverse event following an incorrect decision
  - essentially "Risk" as defined in ISO 14971
  - Therefore, recommend sponsors consider probability of occurrence and severity of harms



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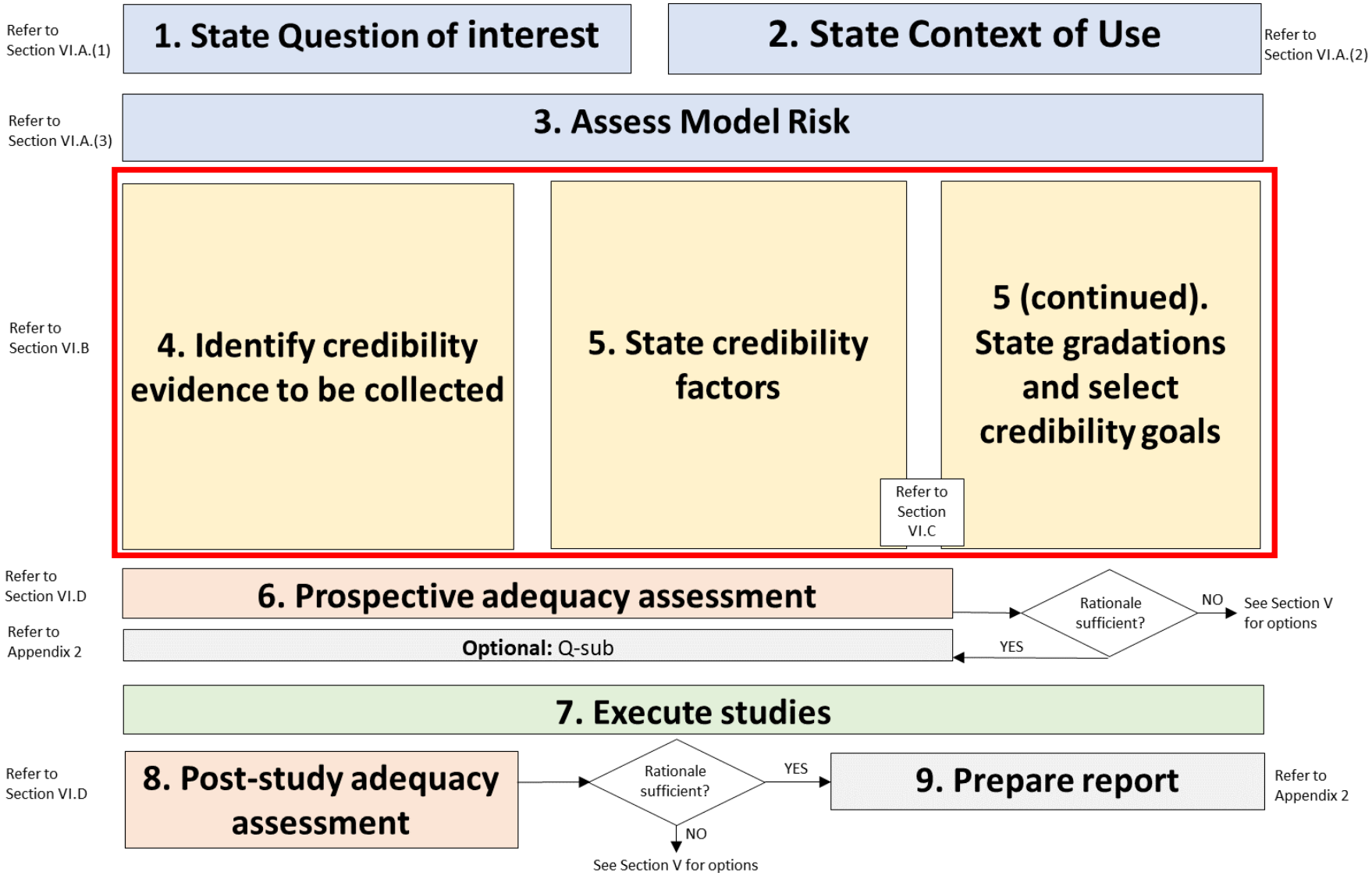
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Step 4: Identify **Credibility Evidence** to be collected

"any evidence that could support the credibility of a computational model"

- Evidence categorization provided (right)
- **Details and device-specific examples** for each category provided in Section VI.B
- Specific **recommendations** for each category in Appendix 1

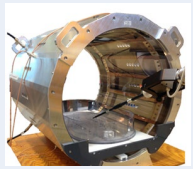
1	Code verification results
2	Model calibration evidence
3	Bench test validation results
4	*In vivo* validation results
5	Population-based validation results
6	Emergent model behavior
7	Model plausibility evidence
8	Calc. verification/UQ using COU conditions

Step 5: **Credibility Factors**

For each set of evidence:

- Define credibility factors (some recommended factors provided)
- For each factor
  - Define a gradation of activities
  - Choose a target level based on the risk assessment

Example

3	Bench test validation results 

Appendix 1 recommends using relevant ASME V&V40 factors

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See ASME V&V40 2018

Gradation from ASME V&V40 2018

(a) A single sample was used.
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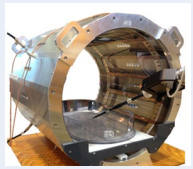

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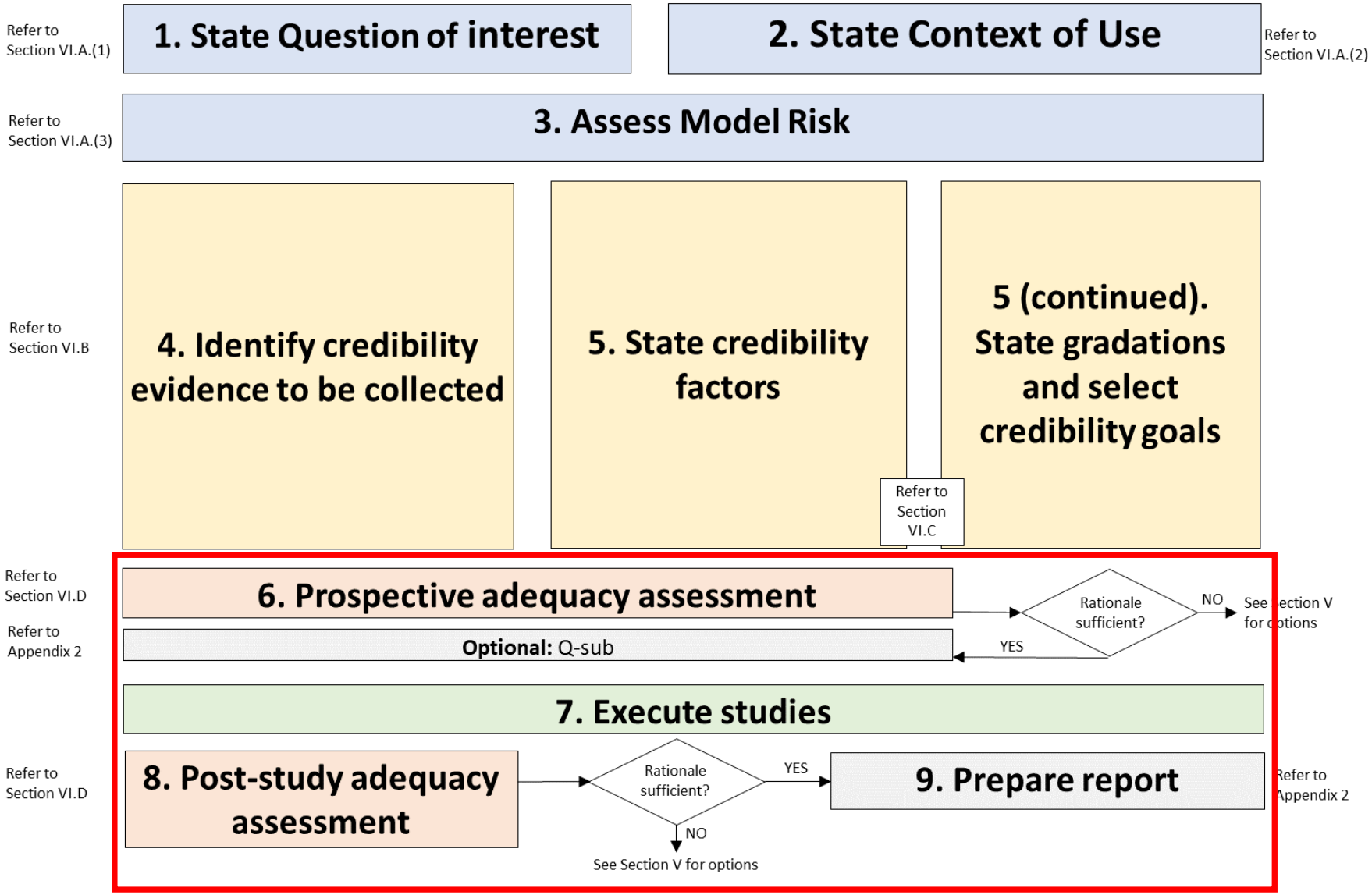
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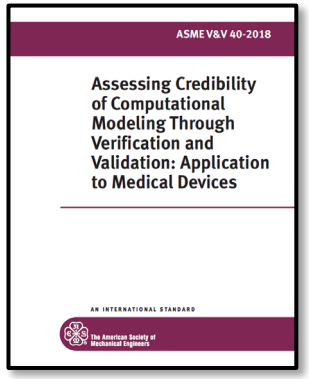
Step 8: Rationale for **Adequacy**

Does the credibility evidence support using the model for the COU given risk assessment?

- Subjective decision based on all available evidence and engineering/clinical judgement
- Considerations
  - All relevant model features tested?
  - If credibility goals not met, consider providing a rationale for why results still adequate
  - How do predictions with uncertainties compare to decision/safety thresholds?
  - Discuss limitations of model

Overview of related efforts

Standard



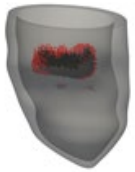
Guidance

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Regulatory Science Tools

Example workflow for **patient-specific models**



Example workflow for **in silico clinical trials**

Discussed today

In silico clinical trials "playbook"

CM&S **mock submission**

Ongoing efforts

Credibility assessment **toolbox**

Detailed credibility assessment **examples**

Possible future efforts

See OSEL website for current regulatory science tools

Regulatory Science Tools

- "A peer-reviewed resource for medical device companies to use where standards and qualified Medical Device Development Tools (MDDTs) do not yet exist"
- Can be used by industry to generate data in support of device safety/effectiveness
- OSEL primary type of deliverable

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Medical Device Material Safety Summaries

CDRH Regulatory Science Priorities

Database for Reference Grade Microbial Sequences (FDA-ARGOS)

Medical Device Regulatory Science Research Programs Conducted by OSEL

Content current as of: 11/06/2023

Regulated Product(s) Medical Devices

Update October 02, 2023: The FDA updated the catalog to add 9 new tools and update 3 tools.

New:

- An In Vitro Blood Flow Loop System for Thrombogenicity Evaluation of Medical Devices and Biomaterials
- CHemical RISk calculators (CHRIS) – Bulk Chemicals (v2)
- CHemical RISk calculators (CHRIS) – Color Additives (v2)
- CHemical RISk calculators (CHRIS) – Extraction Efficiency
- LCD-CT: Low-contrast Detectability (LCD) Test for Assessing Advanced Nonlinear CT Image Reconstruction and Denoising Methods
- Mechanical and Leakage Integrity Testing Protocols for Evaluating the Performance of Tissue Containment Systems Used During Power Morcellation Procedures

See OSEL website for current regulatory science tools

Summary and Key Points

- Mathematical modeling has a plethora of possible regulatory applications for medical devices
  - *In silico* device testing
  - Within device software – including digital twins
  - *In silico* clinical trials

- For CM&S, there are many possible ways to evaluate the models
  - Challenging to develop a coherent and comprehensive regulatory strategy

- FDA is addressing this through Guidance providing a general framework relevant to all modeling fields and submission types
  - Not prescriptive
  - Further assistance for industry provided through Regulatory Science Tools
  - There is a need for future field/device-specific prescriptive standards

Thank you for your attention

Acknowledgments

- Kenny Aycock (FDA)
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- Richard Gray (FDA)
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- Tina Morrison (FDA)
- Steve Niederer (Imperial)