FDA/MDIC Pre-Symposium: FDA CM&S Credibility Guidance Training

Monday, April 15th
2:45 PM – 3:45 PM

Pras Pathmanathan, PhD
Office of Science and Engineering Laboratories, CDRH, FDA
Senior Scientist

#ModSim2024

MDIC Medical Device Innovation Consortium

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

Final Guidance

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

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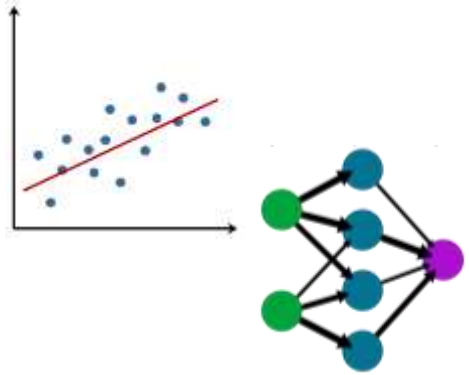
What is computational modeling and simulation (CM&S)?

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



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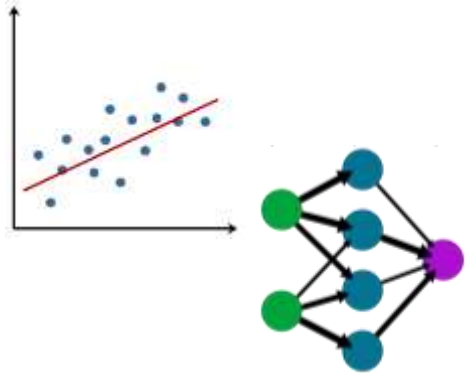


Scope of the guidance

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

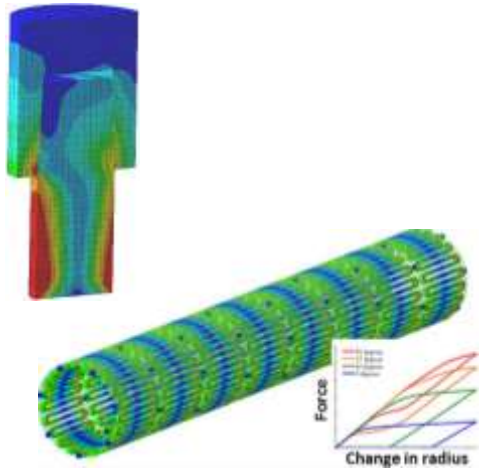
Also out of scope

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

CM&S in regulatory submissions

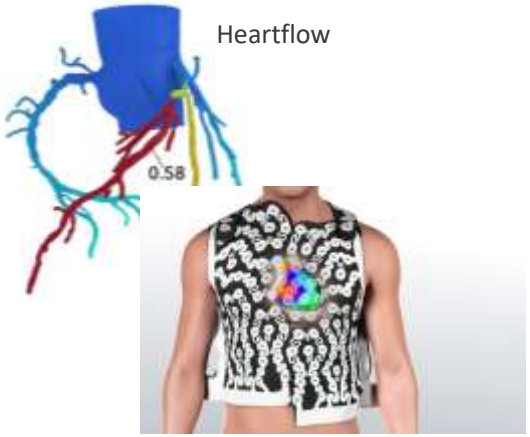
In Silico Device Testing

Simulate device to generate safety/ effectiveness evidence



CM&S in device software

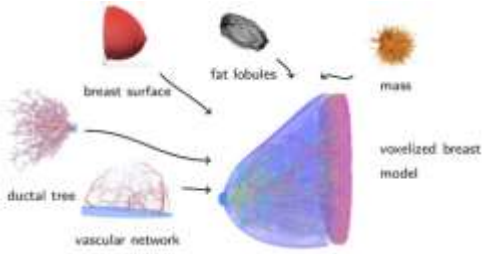
Algorithm in device software takes in patient data and simulates the patient



CardioInsight

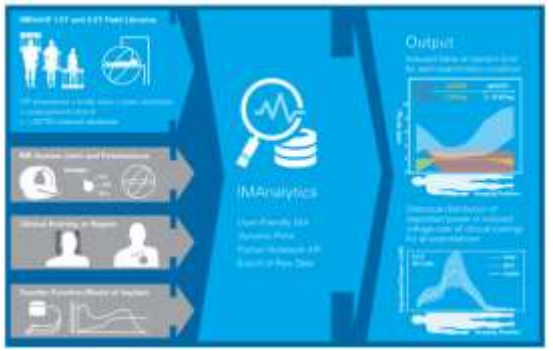
In Silico Clinical Trial

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



OSEL VICTRE project

CM&S-based MDDT



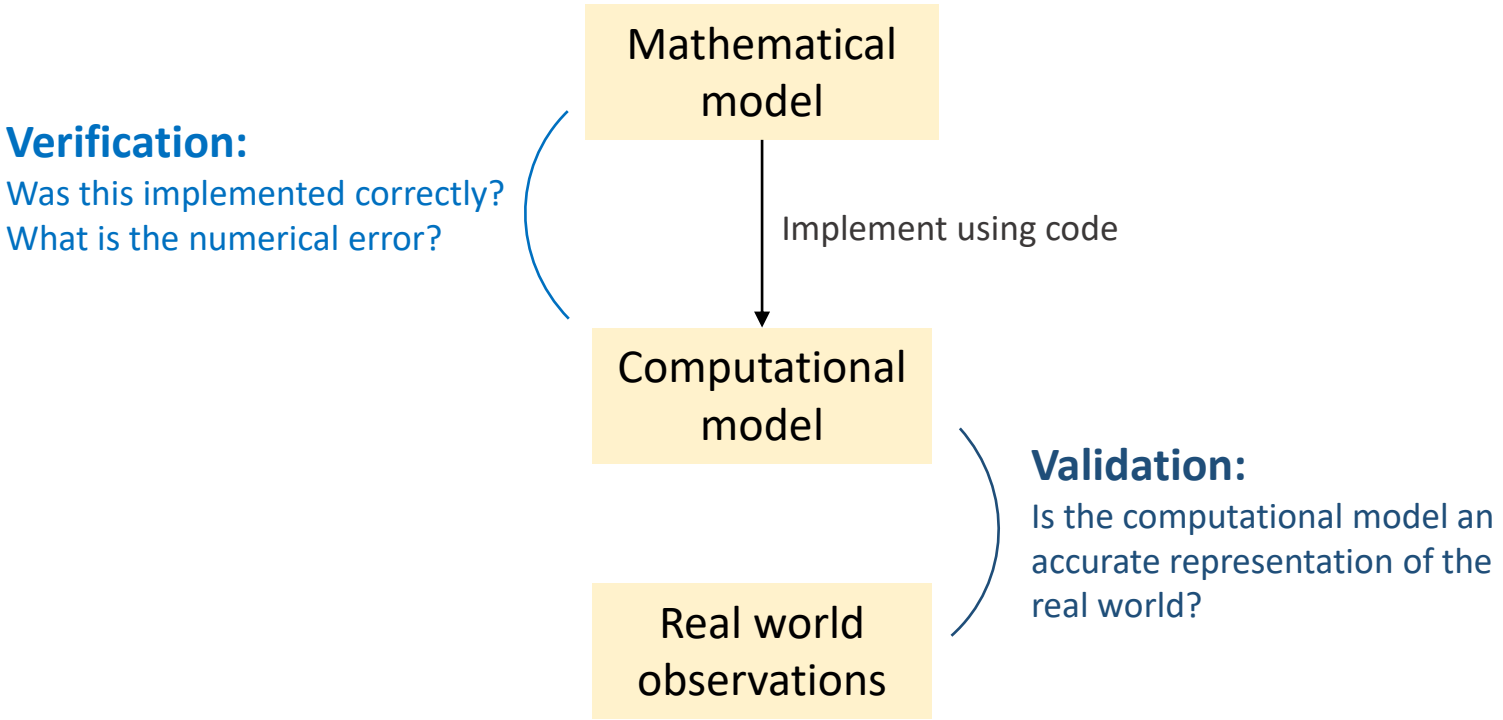
IMAnalytics

510(k), PMA, de novo, IDE, HDE → MDDT

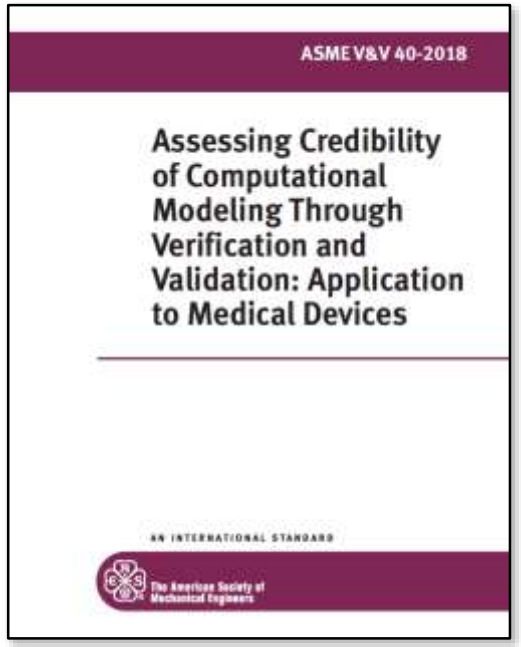
Key Definitions

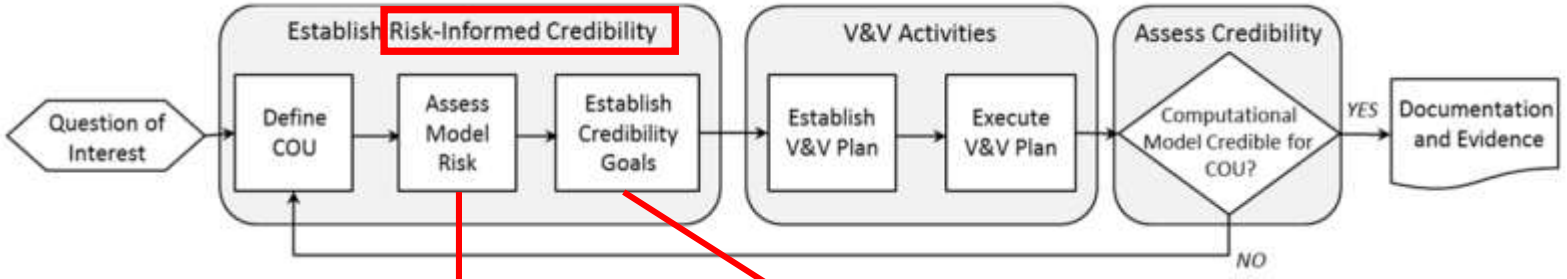
per Credibility Guidance, originally from ASME V&V40 2018:

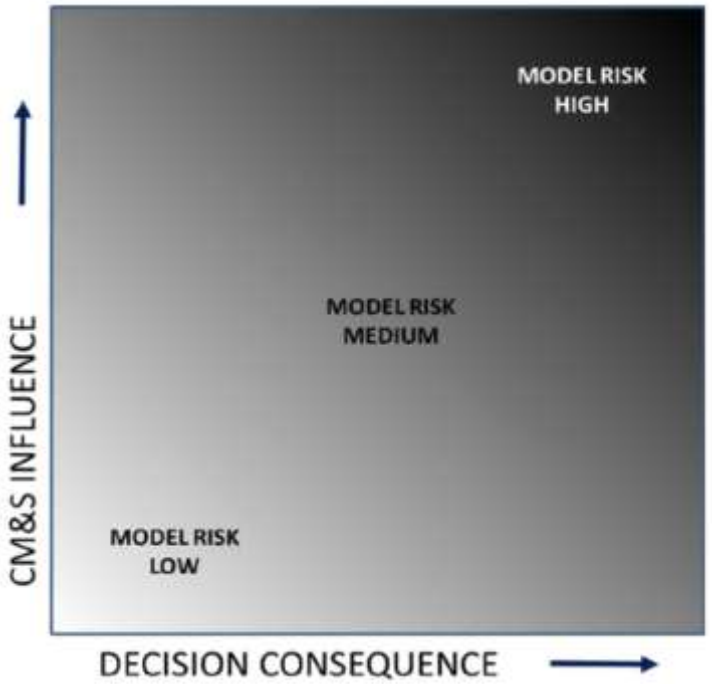
- **Credibility** – "the trust, based on all available evidence, on the predictive capability of a computational model"
- **Context of use (COU)** – "the role and scope of the computational model in answering the question of interest"



ASME V&V40 2018







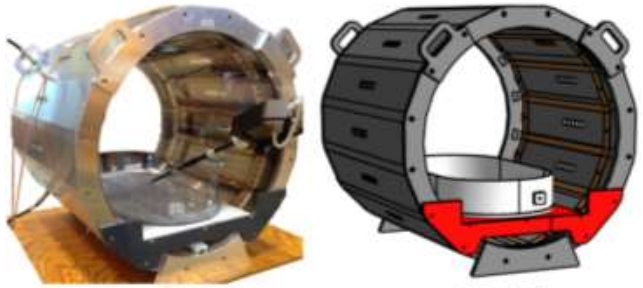
Activities		Credibility Factors
Verification	Code	Software Quality Assurance
		Numerical Code Verification
	Calculation	Discretization Error
		Numerical Solver Error
		Use Error
Validation	Computational Model	Model Form
		Model Input
	Comparator	Test Samples
		Test Conditions
	Assessment	Equivalency 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** 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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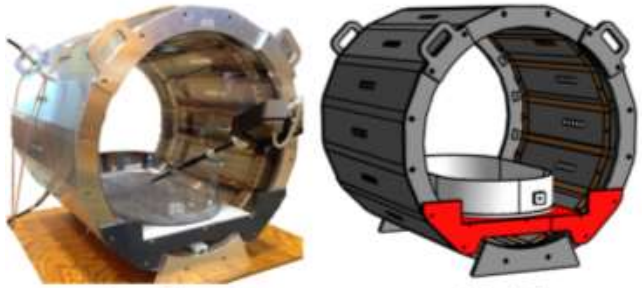

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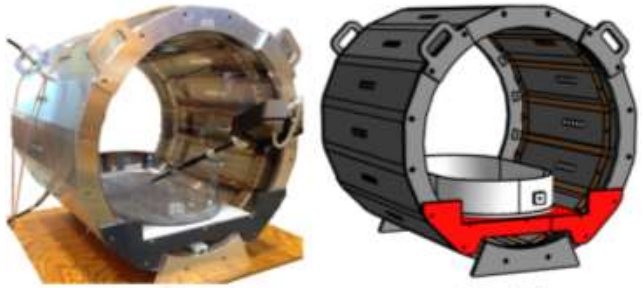
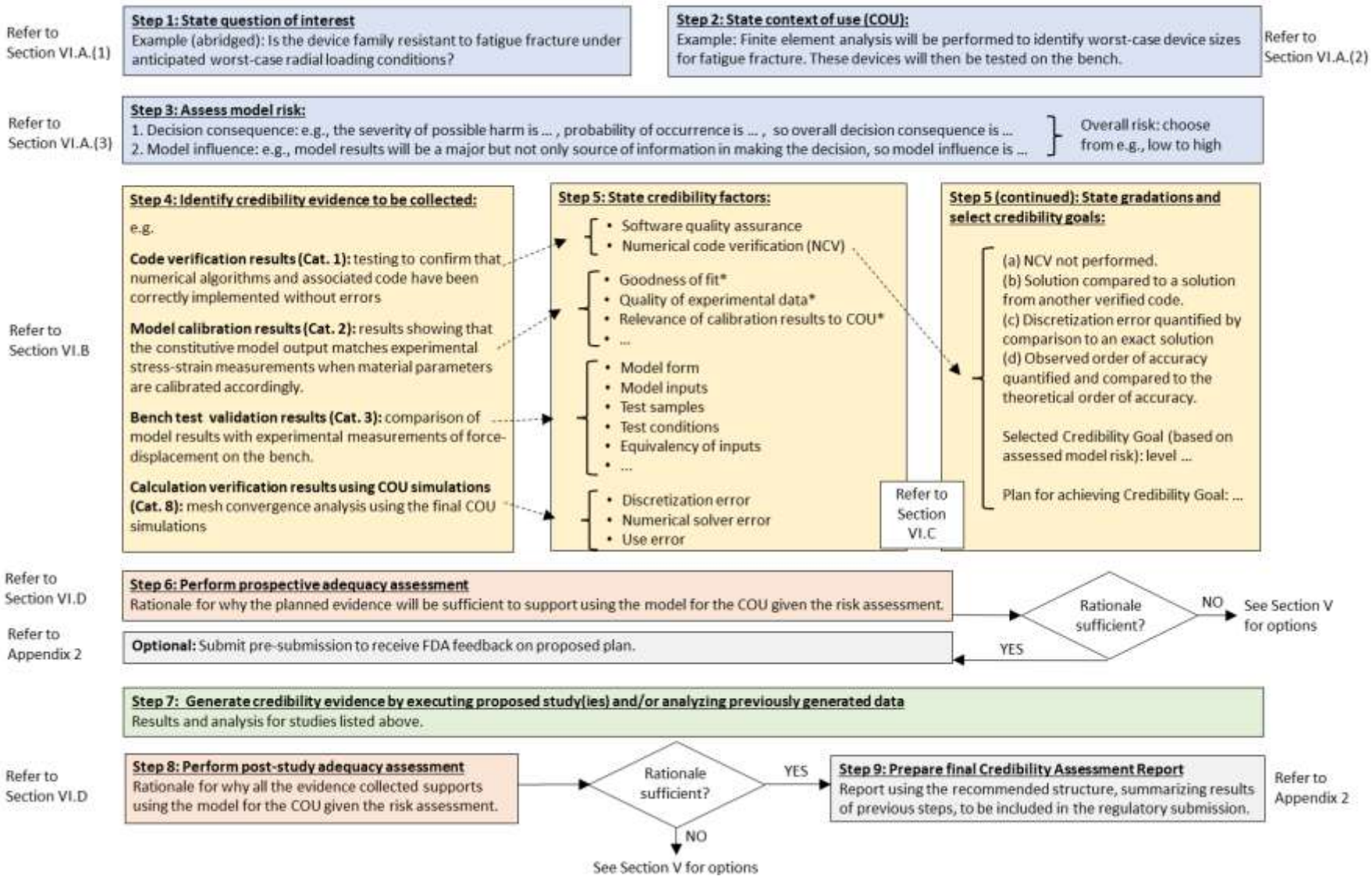


Framework

Guidance Figure 1:



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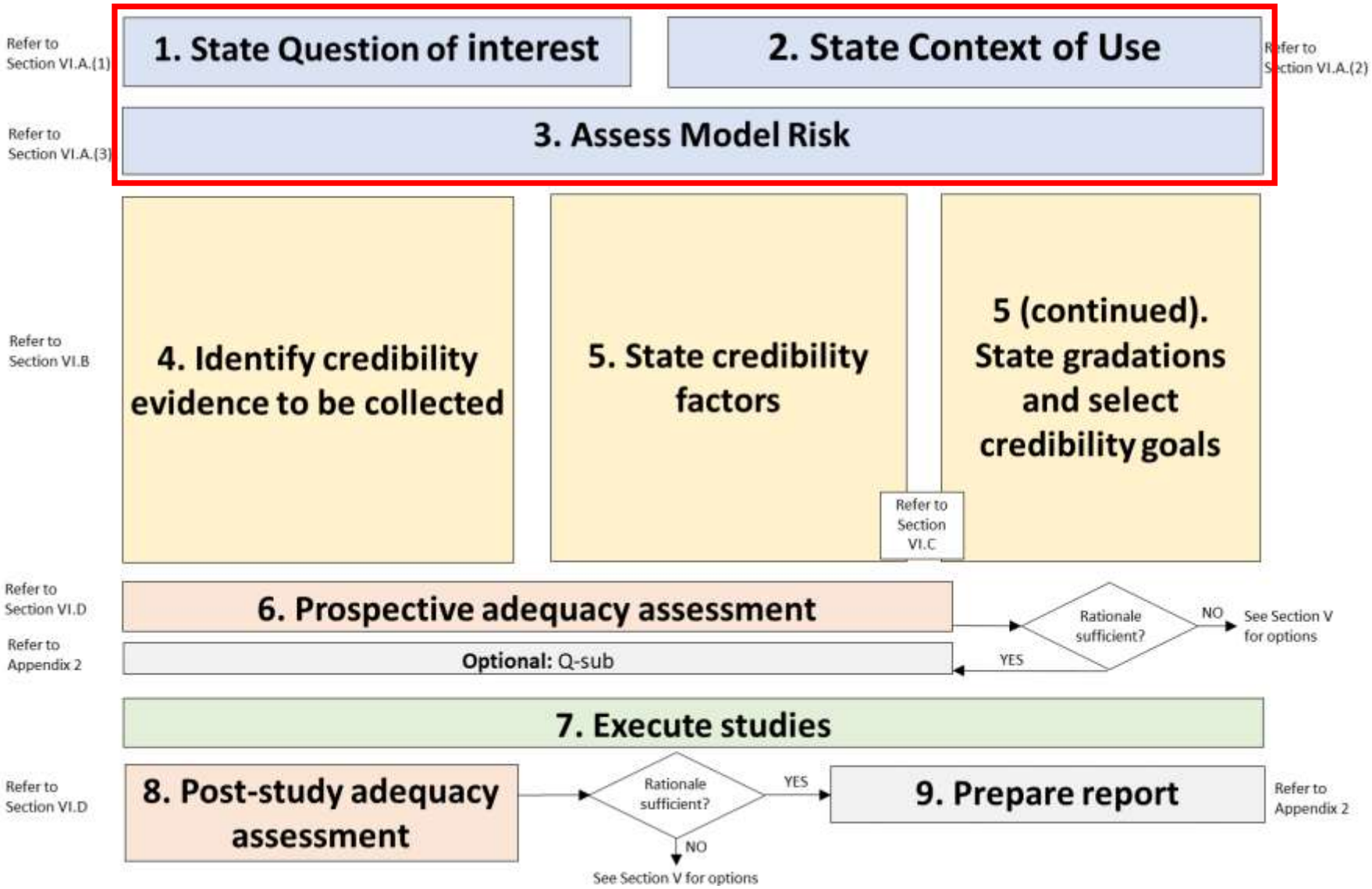

Refer to Section VI.A.(1)
1. State Question of interest
2. State Context of Use
Refer to Section VI.A.(2)
Refer to Section VI.A.(3)
3. Assess Model Risk
Refer to Section VI.B
4. Identify credibility evidence to be collected
5. State credibility factors
5 (continued). State gradations and select credibility goals
Refer to Section VI.C
Refer to Section VI.D
6. Prospective adequacy assessment
Rationale sufficient?
NO
See Section V for options
Refer to Appendix 2
Optional: Q-sub
YES
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

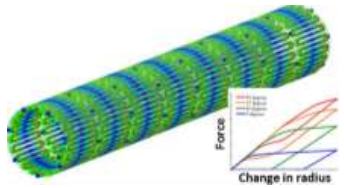
Step 1: state the **Question of Interest**

"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?



Device software function example

What is the electrical activity on the heart epicardial surface?

CardioInsight

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 […]

Device software function example

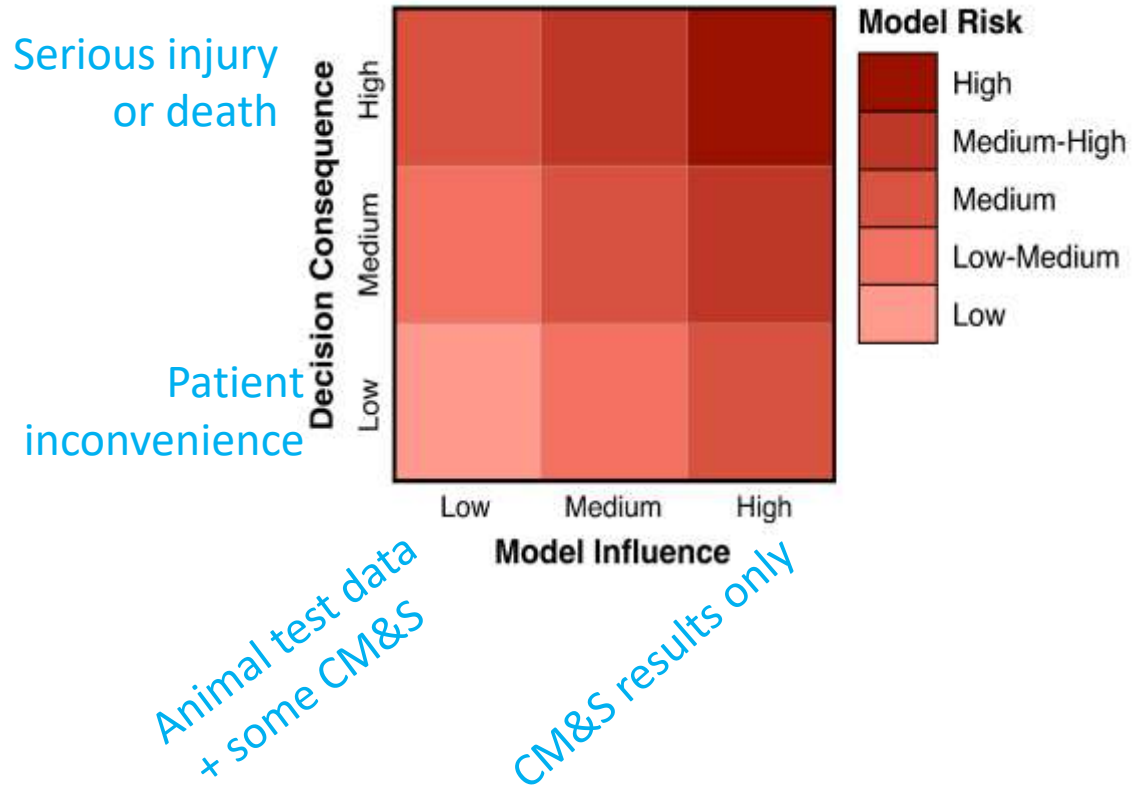
The device generates a patient-specific model of the heart and torso and solves an inverse problem to compute heart surface electrical activity given the recorded body surface electrograms [..]

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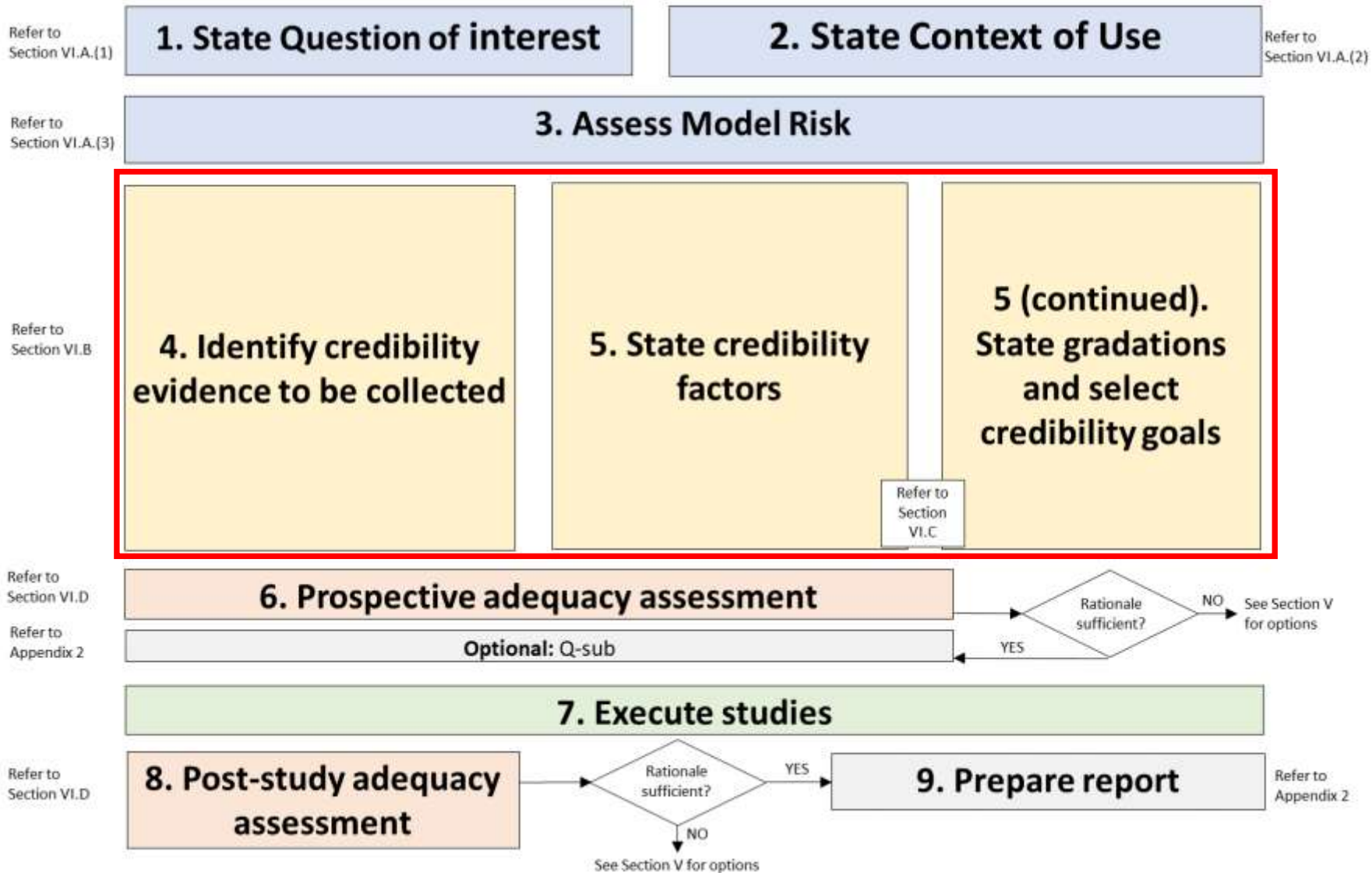
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Step 4: Identify **Credibility Evidence** to be collected

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

1	Code verification results
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- **Details and device-specific examples** for each category provided in Section VI.B
- Specific **recommendations** for each category in Appendix 1

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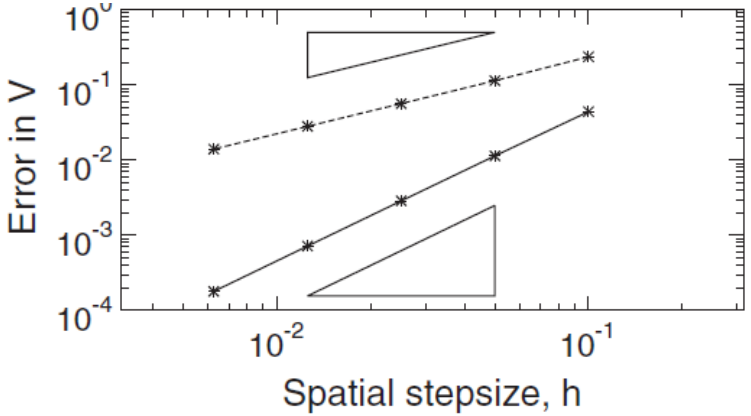
Example: mesh convergence plots



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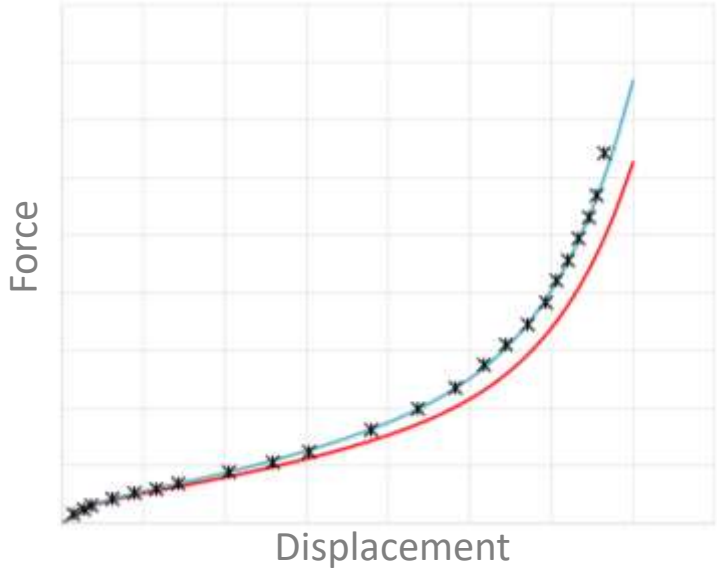

Image: Aventec, Guide to Model Calibration, 2020

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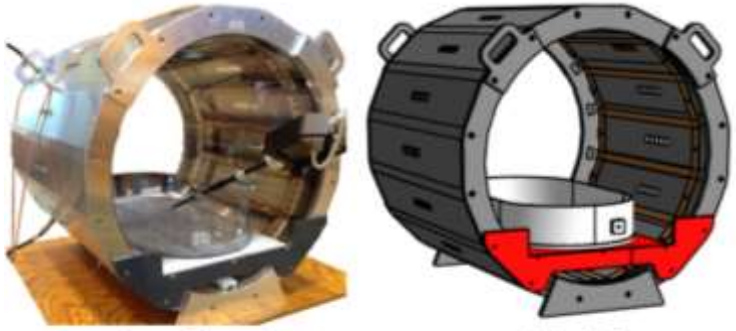
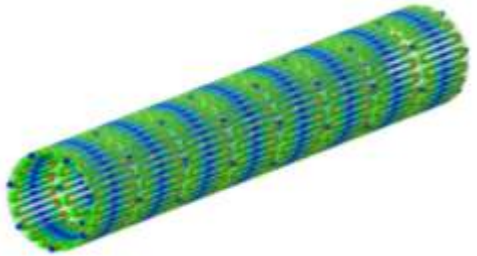
Examples:





Potentially with calculation verification / UQ using these validation models

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Example: validation against animal or clinical data

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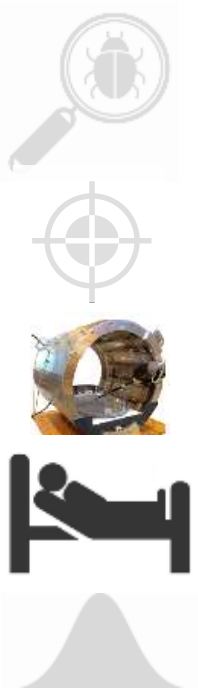

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Prospectively planned validation simulations		
Previously generated validation simulations		

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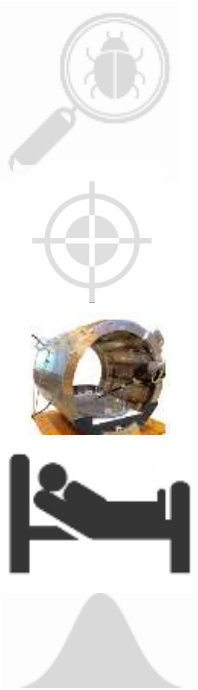

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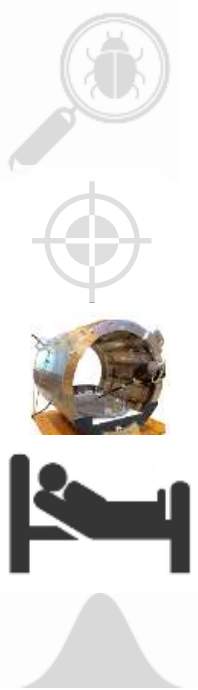

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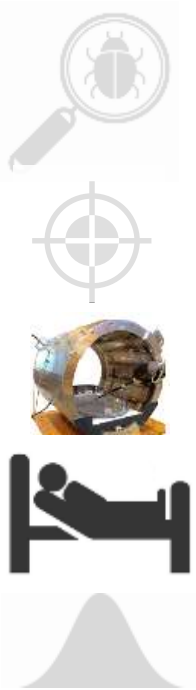

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Previously generated validation simulations	*(Very uncommon)*	Previously generated validation results, e.g., for a previous regulatory submission, or validation results in the literature

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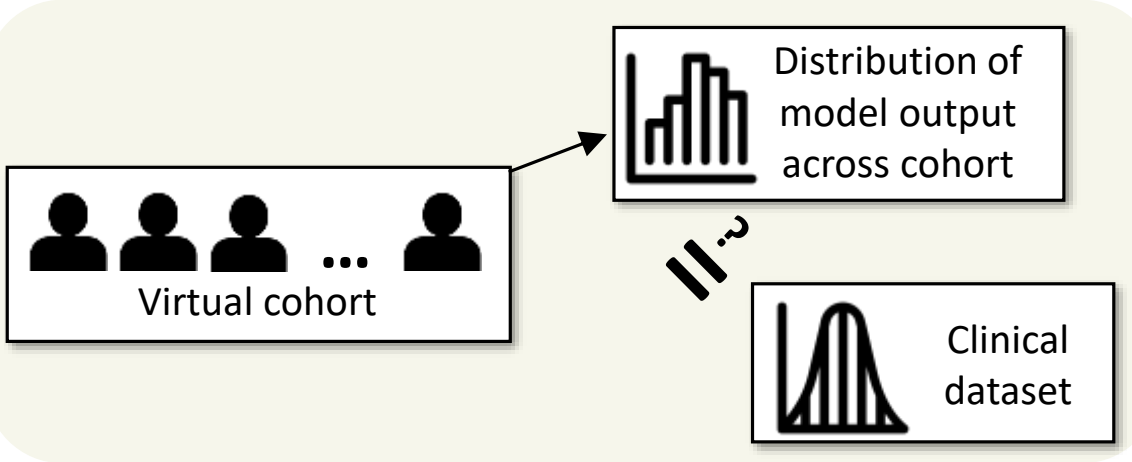

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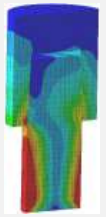
Model of a medical device

- Code verification results (#1)
- Bench validation with supporting calc. verification and perhaps UQ (#3)



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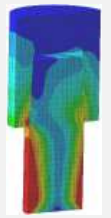

Patient-specific model in device software

- Code verification results (#1)
- *In vivo* validation with supporting calc. verification and perhaps UQ (#4)

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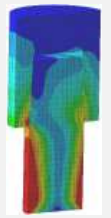
Model of a medical device

- Code verification results (#1)
- Bench validation with supporting calc. verification and perhaps UQ (#3)



Patient-specific model in device software

- Code verification results (#1)
- *In vivo* validation with supporting calc. verification and perhaps UQ (#4)

In silico clinical trial

- Code verification (#1)
- Bench validation (#3) of device model
- *In vivo* validation (#4) of patient model
- Population validation (#5) of virtual cohort

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

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

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

- Sponsors free to choose what to submit, but we recommend cover each of
  - Code verification results (#1)
  - Calculation verification results (#3, #4 or #8)
  - Validation (#3-#5) or other evidence pertaining to ability to reproduce real-world behavior (#2, #6, #7)

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

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

See ASME V&V40 2018

Gradation from ASME V&V40 2018

(a) A single sample was used.
(b) Multiple samples were used, but not enough to be statistically relevant.
(c) A statistically relevant number of samples were used.

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3	Bench test validation results

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	V&V40	Guidance
Cred factors	23 provided	Flexible
Gradations	Flexible but examples provided	Flexible

Example

3	Bench test validation results

Appendix 1 recommends using relevant ASME V&V40 factors

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Gradation from ASME V&V40 2018

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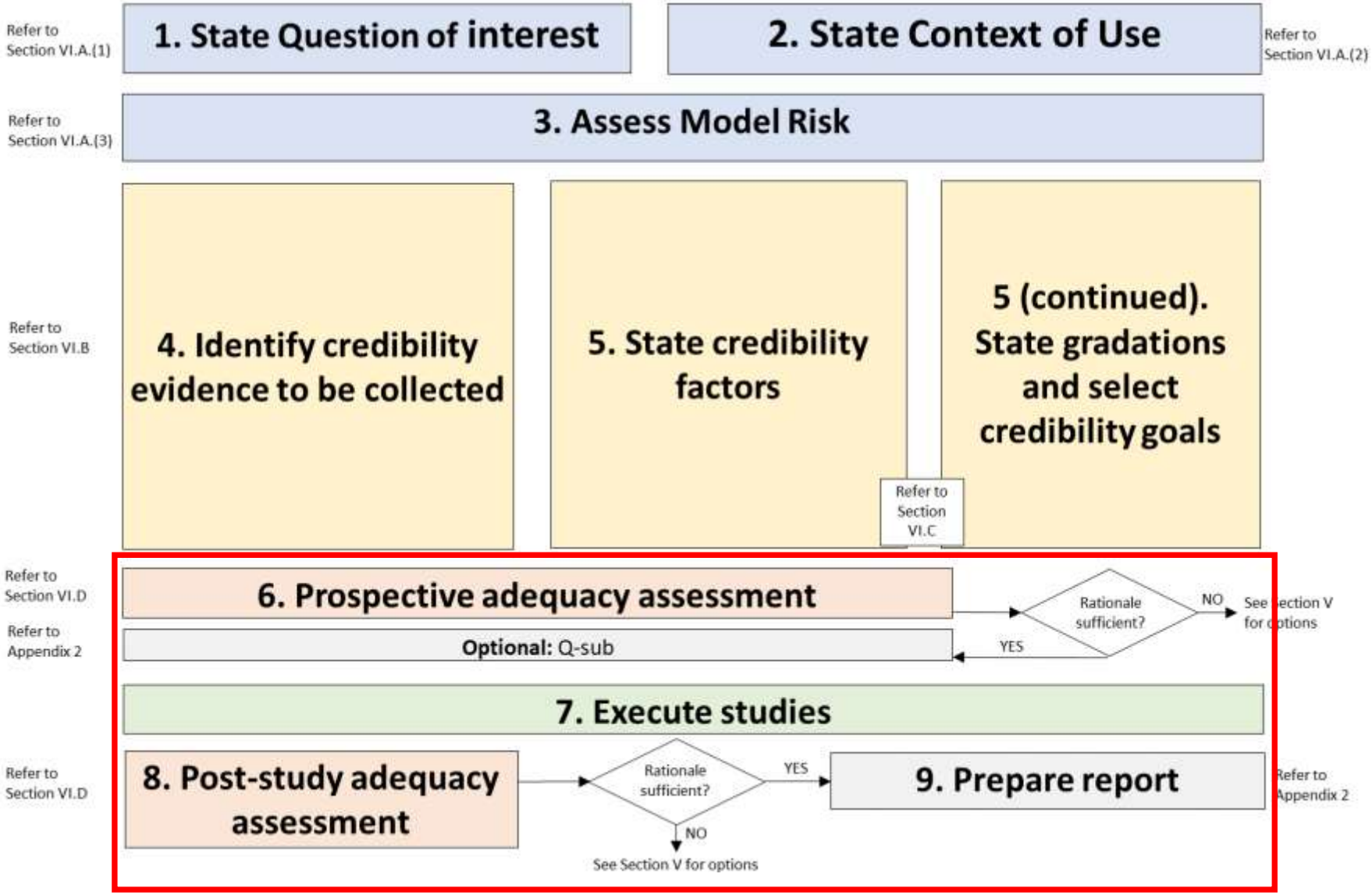
Framework


Refer to Section VI.A.(1)
1. State Question of interest
2. State Context of Use
Refer to Section VI.A.(2)
Refer to Section VI.A.(3)
3. Assess Model Risk
Refer to Section VI.B
4. Identify credibility evidence to be collected
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
Refer to Appendix 2
Optional: Q-sub
YES
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 6 and 8: Rationale for **Adequacy**

Will/does the credibility evidence support using the model for the COU given risk assessment?

- **Step 6: Prospective adequacy assessment**
  - Recommend sponsors generate a rationale for why **planned** evidence with **expected** results will be sufficient
  - Recommend Q-sub to present plan

- **Step 8: Post-study adequacy 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

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Step 9: **Credibility Assessment Report**

- Recommend sponsors provide a self-contained report on model credibility
- Distinct from simulation study results
- Appendix 2 provides a recommended structure
  - Also provides recommended structure for Q-subs

1. **Executive Summary**
2. **Background**
3. **Device Description**
4. **Proposed Indications for Use**
5. **Description of Computational Model**
6. **Model Credibility Assessment**
   a. Summary of overall approach
   b. Question of Interest
   c. COU
   d. Model Risk Assessment
   e. Credibility Evidence. For each:
      i. Categorization of evidence
      ii. Description of evidence
      iii. Chosen credibility factors, gradations, goals/achieved level
      iv. Methods
      v. Results
   f. Post-study Adequacy Assessment
7. **Credibility Assessment Limitations**
8. **Conclusions**

Summary and Key Points

- Guidance is relevant to first principles (e.g., physics-based) models or FP components of hybrid models
  - Not relevant to standalone AI/ML
- For these models, there is a wide range of possible evaluation methods
- Guidance provides a general framework relevant to all OHTs, submission types, and modeling field
  - Necessarily flexible / not prescriptive
- Based on but extends ASME V&V40 2018
  - Can follow this guidance by following V&V40 (and doing adequacy assessment)
- Guidance framework is a nine-step process:
  - 1-3: define how model will be used and assess risk of using model
  - 4-6: prospective planning and recommended Q-sub
  - 7-9: execution, justification, report

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Thank you for your attention

Recorded FDA webinar available at CDRH Learn

www.fda.gov/Training/CDRHLearn

- Start Here/The Basics! - *(Updated module 5/13/22)*
  MDUFA Small Business Program, Registration and Listing
- How to Study and Market Your Device - *(New module 12/23/21)*
  510k, De Novo, IDE, PMA, HUD/HDE, Q-Submissions, Standards, Classification
- Postmarket Activities - *(New modules 9/22/21)*
  Quality System, Exporting, Device Recalls, MDR, Inspection - Global Harmonization
- Unique Device Identification (UDI) System
- Specialty Technical Topics - *(Updated module 6/24/22)*
- Radiation-Emitting Products - *(Updated module 7/27/22)*
- 510(k) Third Party Review Program (for Third Party Review Organizations)
- Industry Basics Workshop Series

OSEL Regulatory Science Tools provide supporting resources