U.S. FOOD & DRUG ADMINISTRATION

Welcome To Today's Webinar

Thanks for joining us!
We'll get started in a few minutes

Today's Topic:
Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions, Final Guidance

January 11, 2024

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

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Office of Science and Engineering Laboratories

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U.S. Food and Drug Administration

Final Guidance

- **Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions**
  - www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

Learning Objectives

- Define computational modeling and simulation (CM&S) and state scope of guidance
- Describe key points and approach of guidance
- Outline the framework for credibility assessment

CM&S and Scope of Guidance

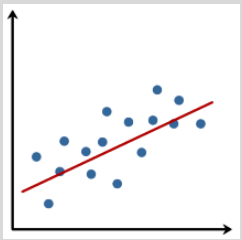
What is CM&S?

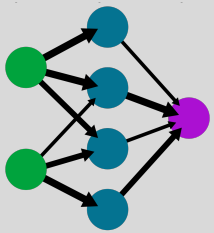
Data-driven models
- Statistical methods
- Machine learning (ML)

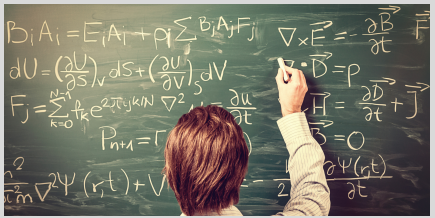
Hybrid methods
- First-principles model with data-driven sub-model(s)
- Train ML model to first-principles model results

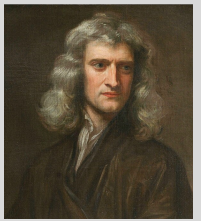
First-principles models
- Physics-based models
- Mechanistic models

Mathematical models









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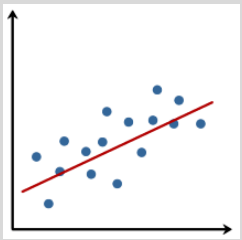
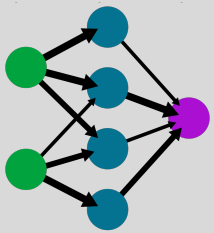
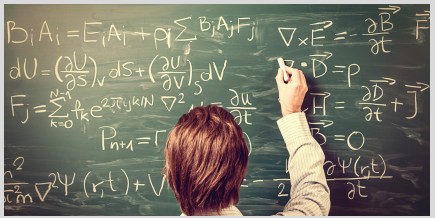
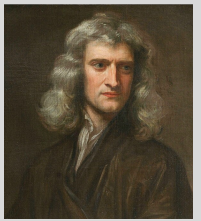




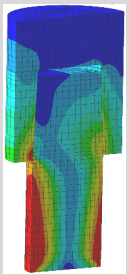




CM&S in Regulatory Submissions

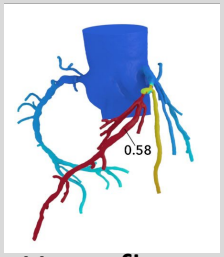
In Silico Device Testing

Simulate device to address safety / effectiveness question



CM&S in device software

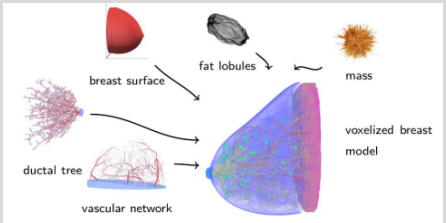
Device takes in patient data and simulates patient



Heartflow

In Silico Clinical Trial

Simulate device on 'virtual cohort' of simulated patients



OSEL VICTRE project

CM&S-based MDDT

CM&S tool relevant to multiple devices

Scope

In Scope

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

Out of Scope

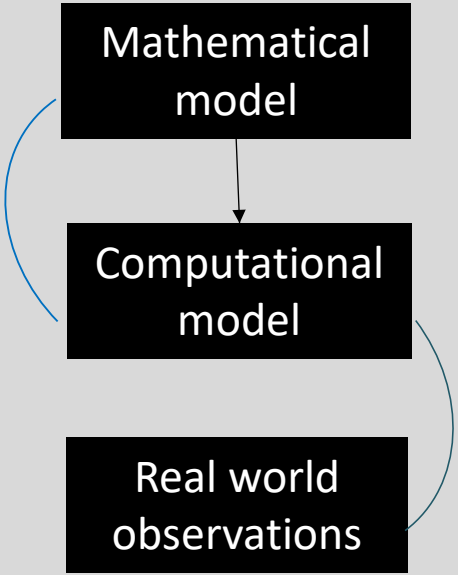
- Standalone statistical or data-driven models
- Models with no simulation, such as anatomical models
- How to perform modeling studies
- Technical details for how to perform credibility assessment
- Specific level of credibility needed for regulatory submissions

Key Definitions

Paraphrased from Guidance and American Society of Mechanical Engineers (ASME) Verification & Validation (V&V) 40-2018 Standard:

- **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

Verification:
Was this implemented correctly?
What is the numerical error?



Validation:
Is the computational model an accurate representation of the real world?

Key Points and Approach

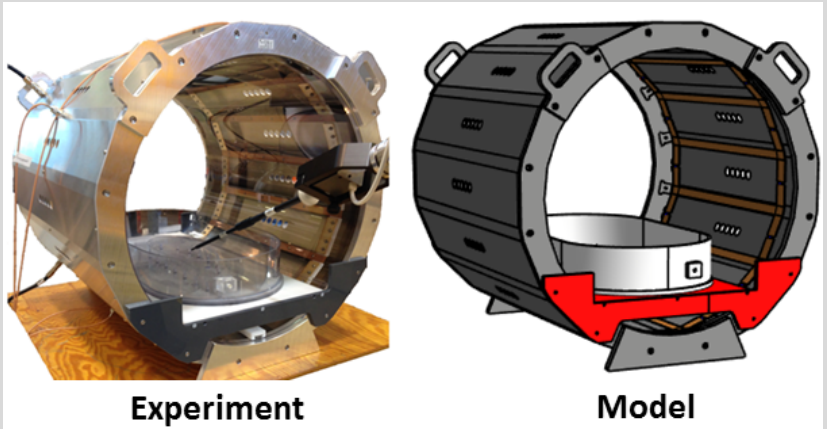
Key Points and Approach

- Guidance is consistent with ASME V&V40-2018
  - **Risk-informed** credibility assessment
  - Emphasis on **question of interest, context of use** and **model risk**
  - Guidance includes additional recommendations on information to provide in a regulatory submission

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

Key Points and Approach (cont'd)

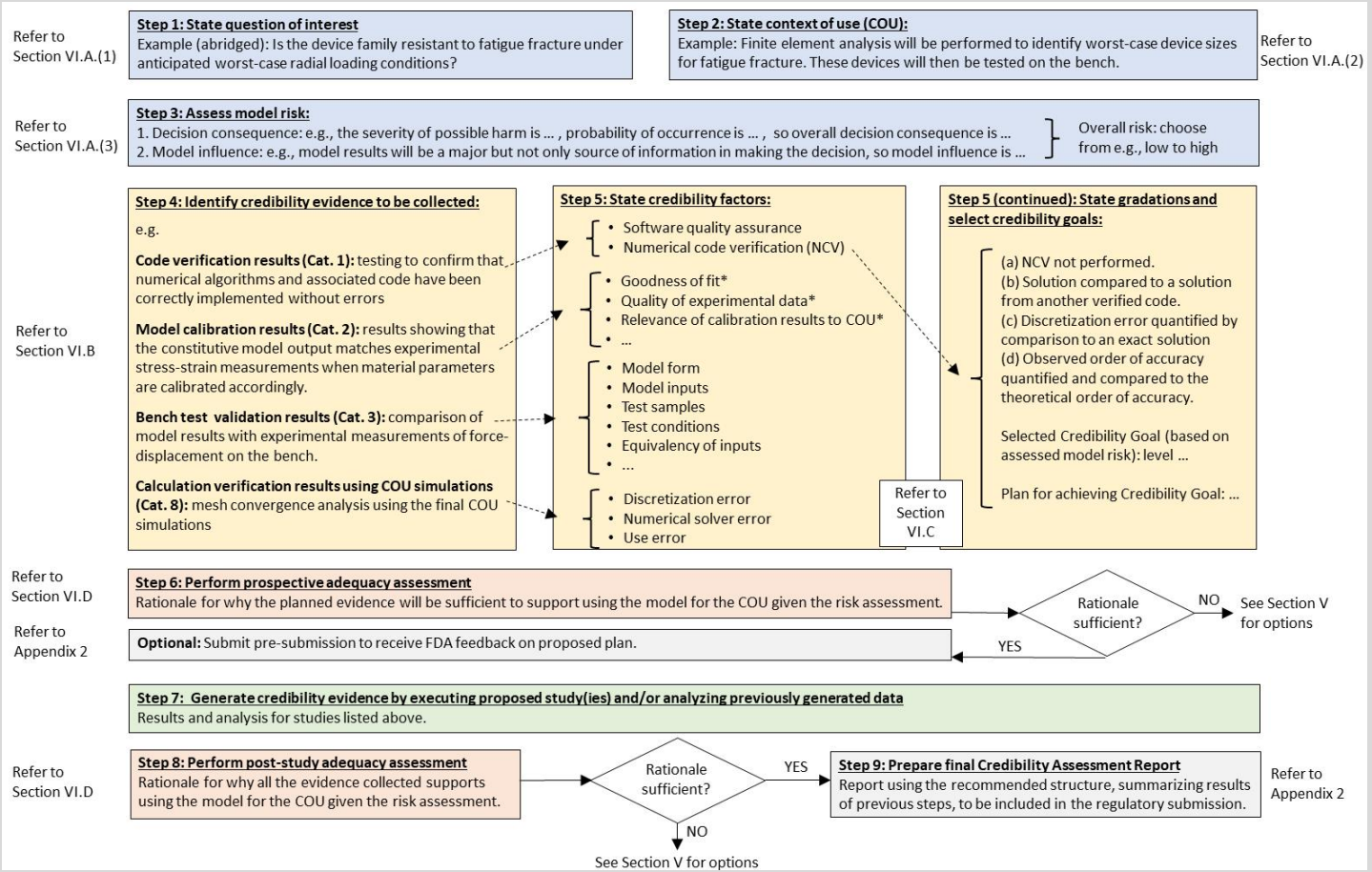
- Framework extends approach of ASME V&V40-2018
  - ASME V&V40 implicitly assumes validation against prospective well-controlled bench tests



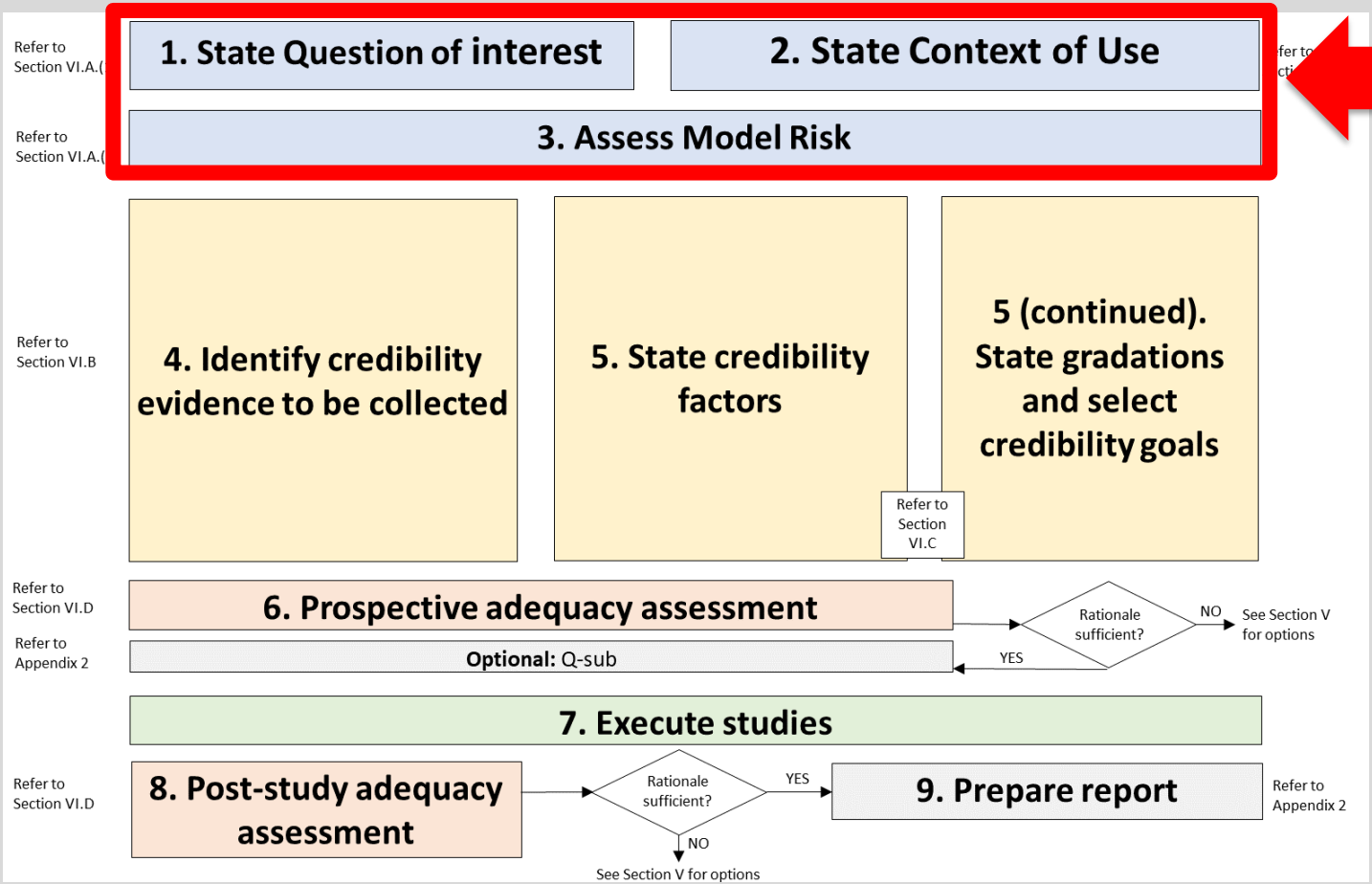
Overview of Framework

Framework

Guidance Figure 1



Framework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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 ("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 (such as bench, animal, or clinical) will be used to answer the question of interest

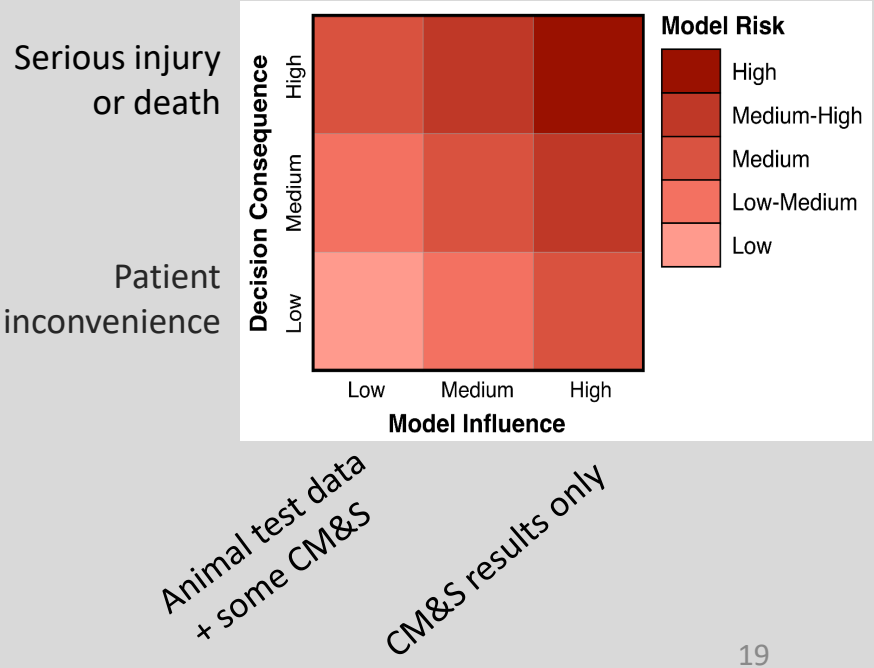
Device testing example

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"

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



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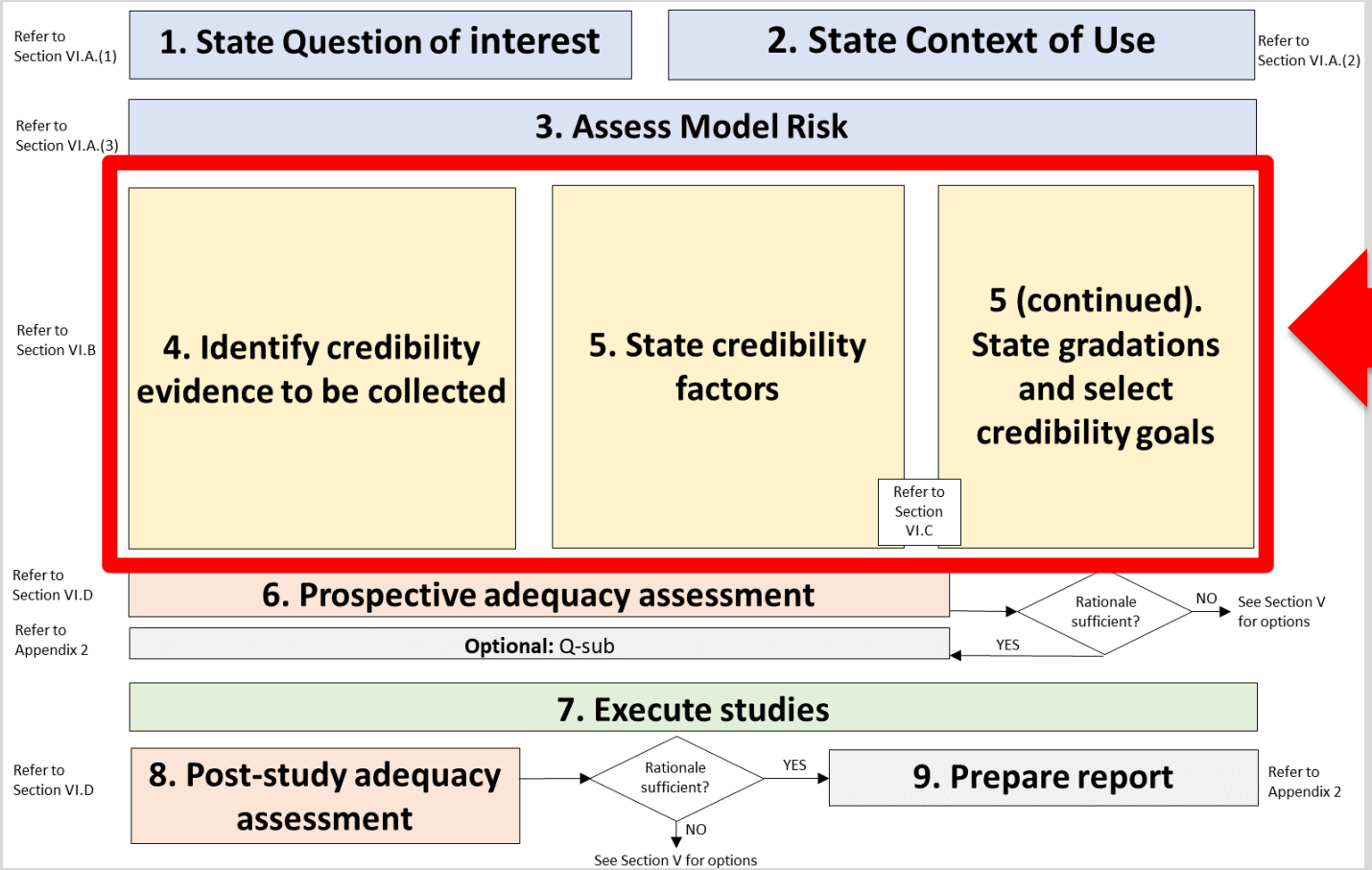
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Step 4: Identify **Credibility Evidence** to be collected

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

Categorization

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





- **Details and examples** in Section VI.B
- **Recommendations** in Appendix 1
- Recommend submissions covers:
  - 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)

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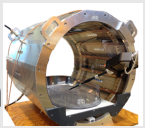
Step 5: **Credibility Factors**

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

Example

3	Bench validation 

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

Gradation

(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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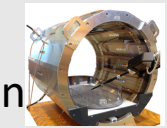
3	Bench validation 

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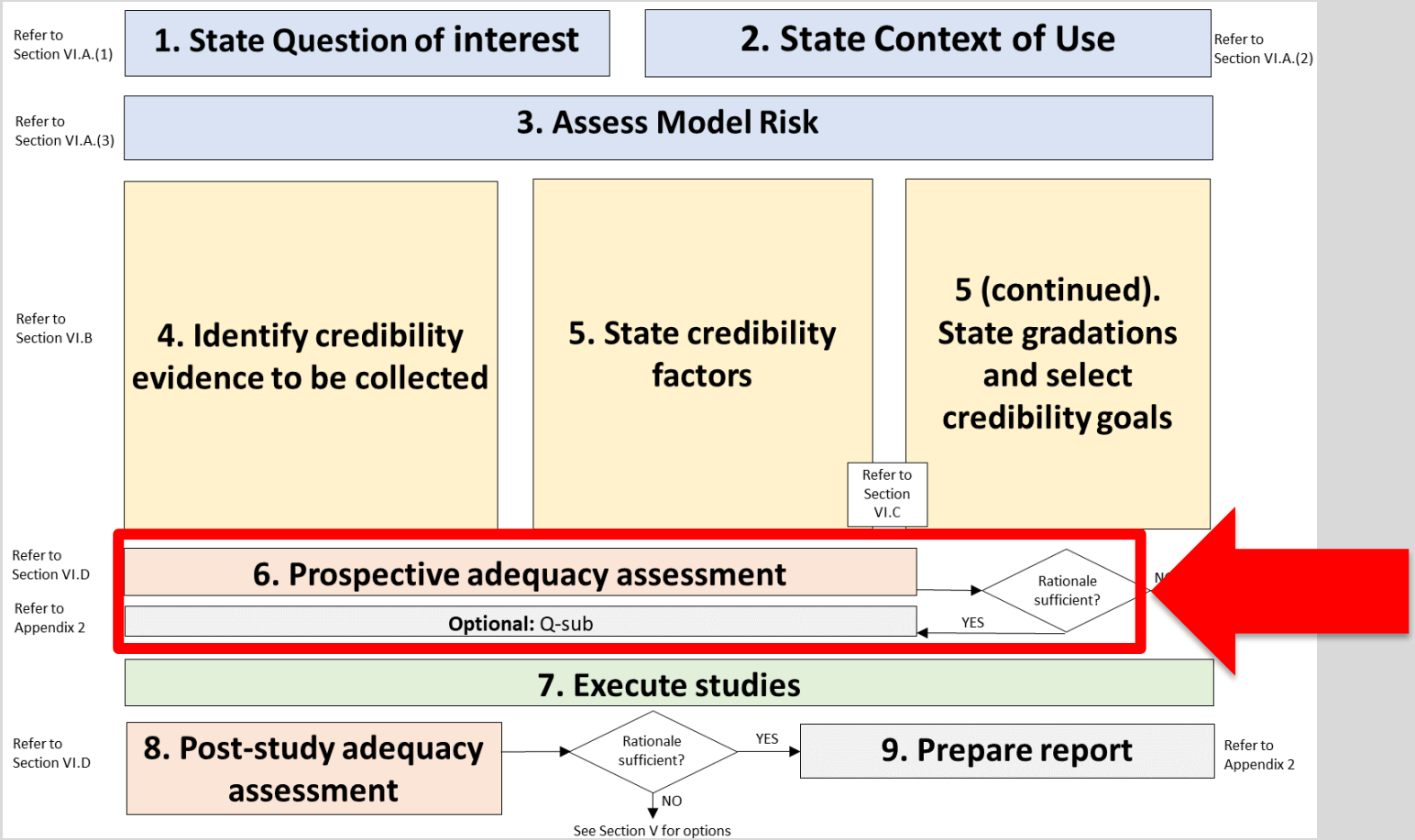
Framework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YES
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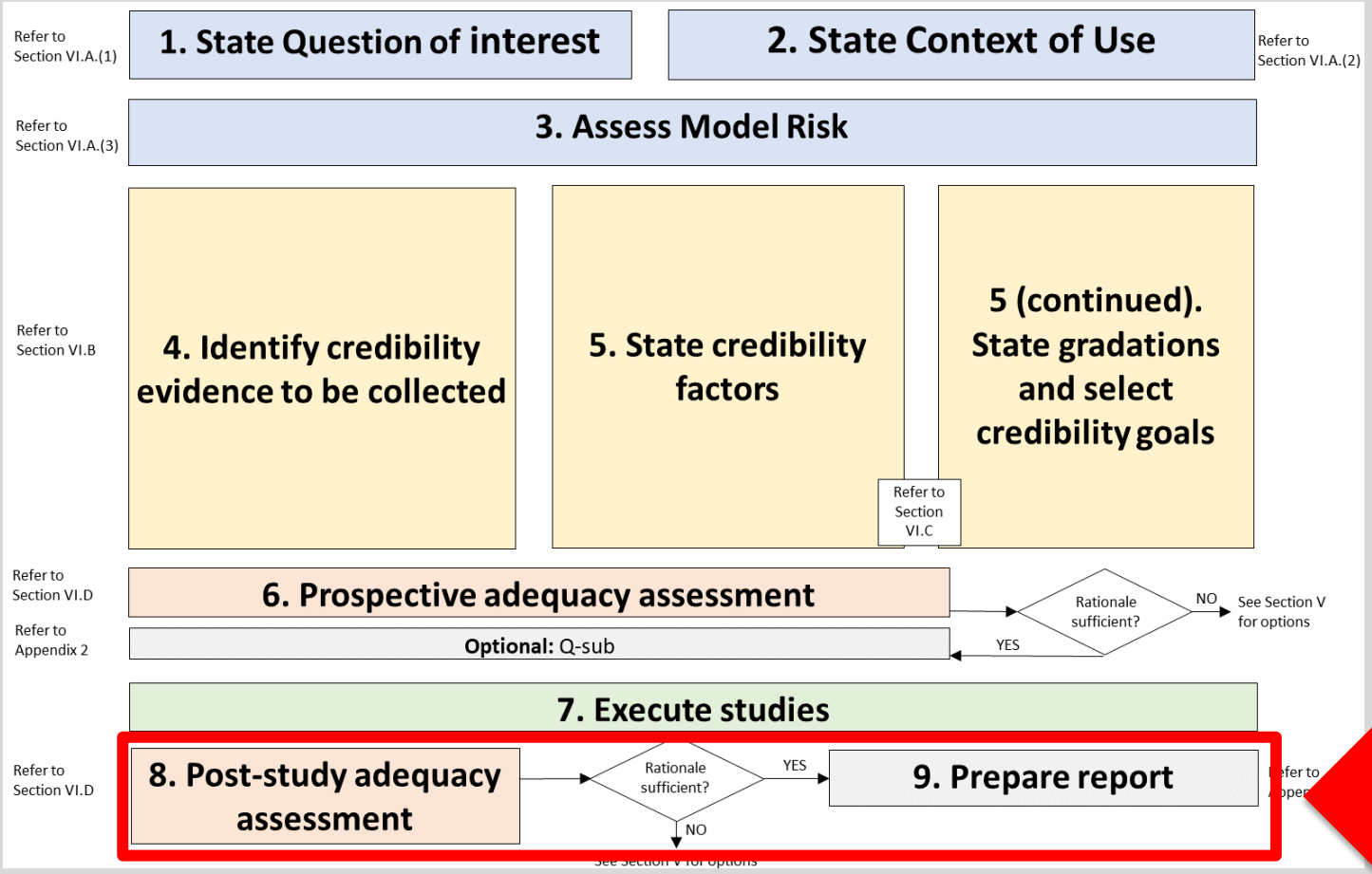
NO
See Section V for options

Step 6: Rationale for **Adequacy**

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

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

Framework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Step 8: Rationale for **Adequacy**

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

- **Step 8: Post-study adequacy assessment**
  - Decision based on all available evidence and engineering/clinical judgement
  - Considerations
    - All relevant model features tested?
    - If credibility goals not met, consider rationale for why results still adequate
    - How do predictions compare to decision/safety thresholds?
    - Discuss limitations

Step 9: **Credibility Assessment Report**

- Recommend self-contained report on model credibility
  - Distinct from simulation study results
- Recommended structure in Appendix 2
  - Also provides recommended structure for Q-Submissions

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**

Resources

Slide Number	Cited Resource	URL
3	Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions	www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions
10	ASME V&V40-2018	www.asme.org/codes-standards/find-codes-standards/v-v-40-assessing-credibility-computational-modeling-verification-validation-application-medical-devices

Summary

- Guidance is relevant to first principles (such as physics-based) models or first principles components of hybrid models
- Guidance provides a general framework relevant to all modeling fields and submission types
- Guidance framework is a nine-step process
  - Steps 1-3: define how model will be used and assess risk of using model
  - Steps 4-6: prospective planning and possible Q-Submission
  - Steps 7-9: execution, justification, report


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Additional Panelists

Brent Craven
Senior Science Advisor
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Office of Science and Engineering Laboratories

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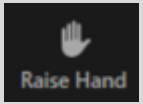
Finn Donaldson
Team Lead
Peripheral Interventional Devices
Office of Health Technology 2
Office of Product Evaluation and Quality

Let's Take Your Questions

- **To Ask a Question:**
  - Raise your hand in Zoom 

  - Moderator will announce your name and invite you to ask your question
  - Unmute yourself when prompted in Zoom to ask your question

- **When Asking a Question:**
  - Ask one question only
  - Keep question short
  - No questions about specific submissions

- **After Question is Answered:**
  - Mute yourself and lower your hand
  - If you have more questions - raise your hand again

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