



ABioM: A Management Framework for Supporting Adaptive and Iterative VVUQ Efforts in Biomedical Modeling

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Disclaimer:

This work is strictly for research and is not a guidance or regulatory document.

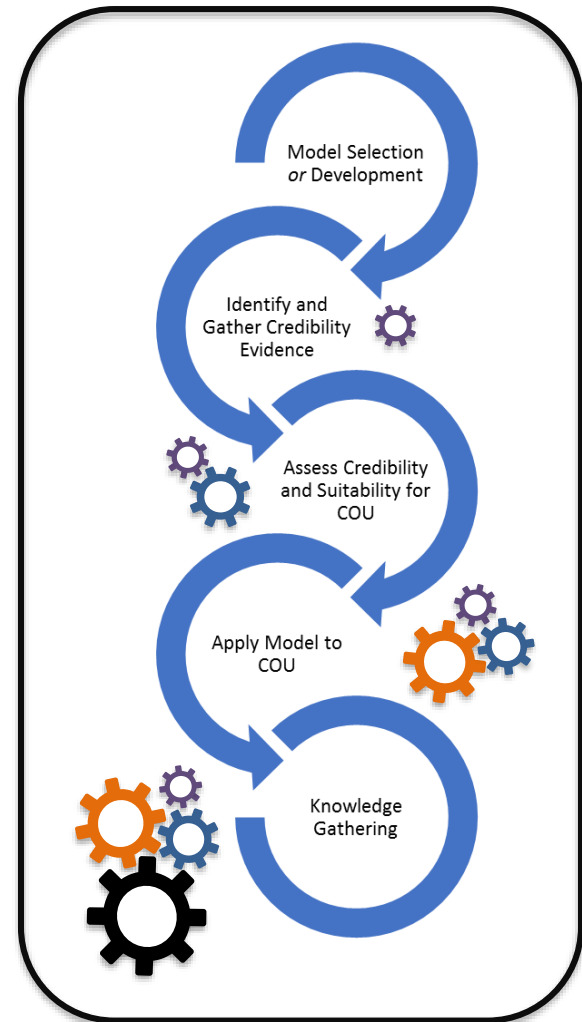
Outline

- Background
- Concepts
- Architecture
- Demo
- Application
- Summary

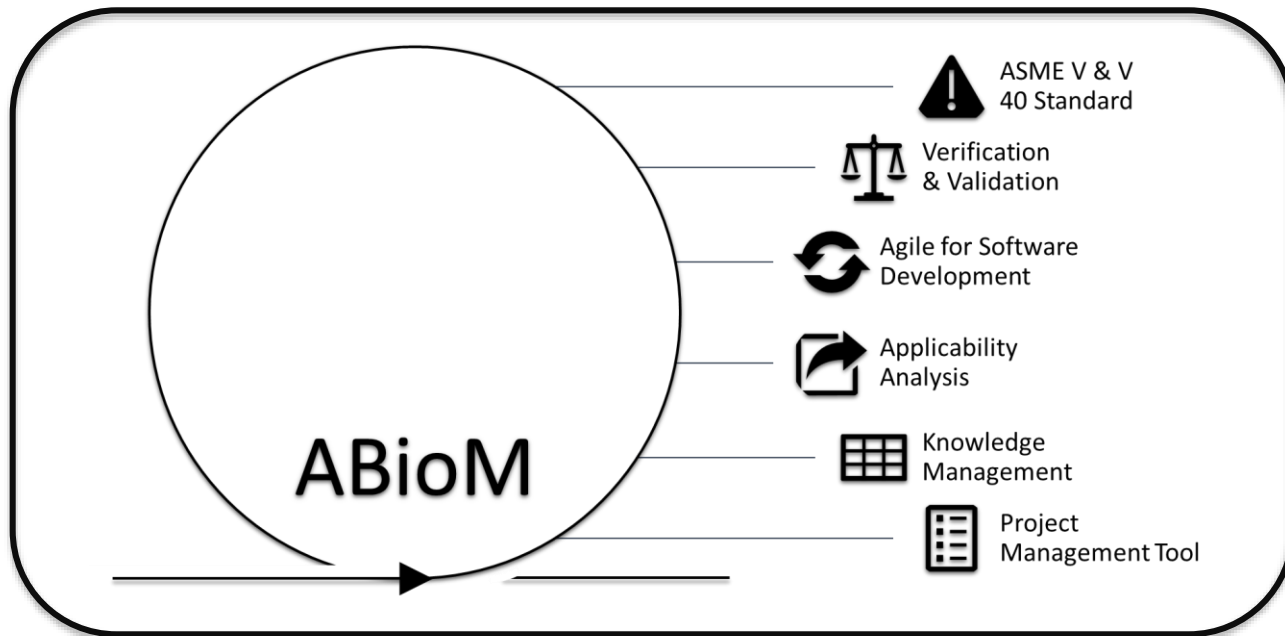
Motivation

Developing an Electronic Drug Delivery System (**EDDS**) Computational Model:

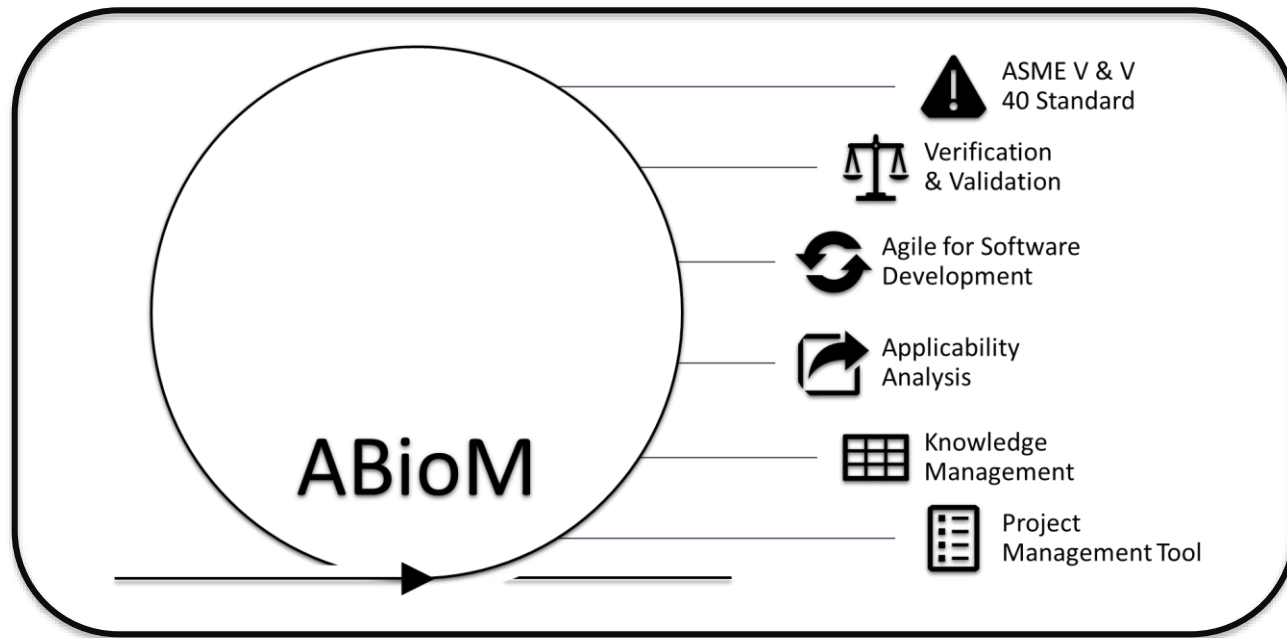
- Credibility Plan and Assessment using the ASME V&V40 Standard
- Integrates Credibility building into the modeling project lifecycle
- Inline with FDA Guidelines
- Follows the actual process for a translational model



Agile for BioMedical Modeling (ABioM)



Agile for BioMedical Modeling (ABioM)



Risk



Credibility



Adaptability



Applicability



Knowledge

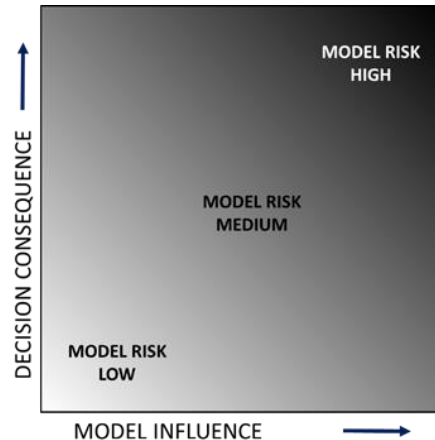
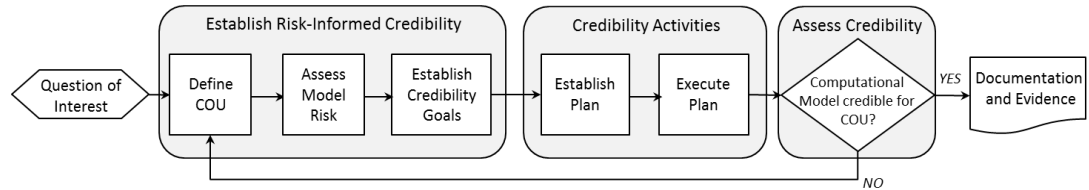


Project

ASME V&V 40 Standard

ABioM reinforces

- Risk-Informed
 - Decision making
 - Credibility assessment
- Relevant evidence collection
- Appropriate Computational Model Use
- Clear Communication
 - Credibility plan
 - Credibility activities



	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 Inputs
	Comparator	Test Samples Test Conditions
	Assessment	Equivalency of Input Parameters Output Comparison
Applicability		Relevance of the QOI's Relevance of the Violation Activities to the COU



Risk



Credibility



Adaptability



Applicability



Knowledge



Project

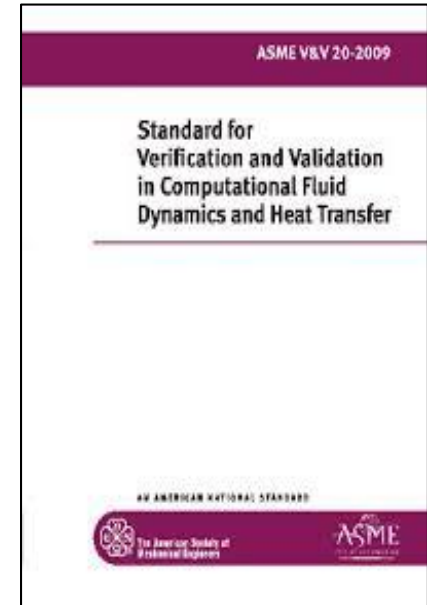
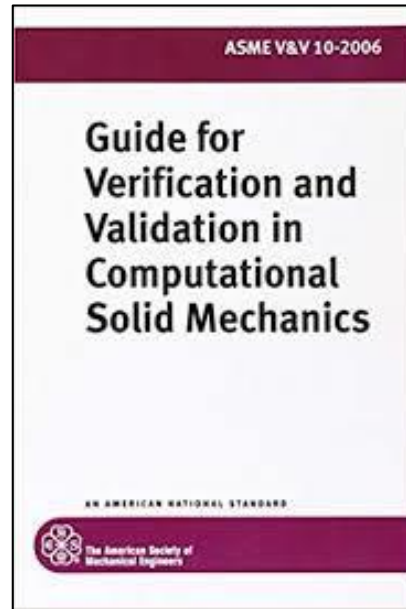
Verification & Validation (V&V)

ABioM does *not*

- Explain how to conduct V&V efforts

ABioM does

- Allow for integration of relevant V&V activities
- Ensure Verification and Validation efforts are conducted or addressed
- Compare the V&V efforts completed with the specified Credibility Goals



Risk



Credibility



Adaptability



Applicability



Knowledge



Project

Agile for Software Development

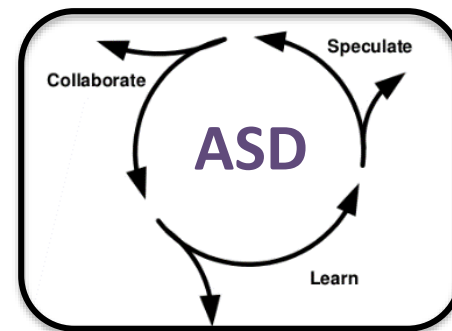
ABioM is derived from:

- Adaptive Software Development (ASD)
 - Modeling Project Lifecycle
- Scrum
 - Team management
 - Collaboration

10. **Simplicity** – *the art of maximizing the amount of work not done* – is essential.

12 Principles

1. Early and **continuous** delivery of **valuable scientific discoveries**
2. Even in late development **welcome changing requirements**
3. Knowledge is **delivered frequently** (weeks rather than months)
4. Close, **daily cooperation** between researchers
5. Projects are built around **motivated individuals**, who should be trusted
6. The best form of communication is **face-to-face conversation** (co-location)
7. The primary measure of **progress is scientific discoveries**
8. Sustainable research, able to maintain a **constant pace**
9. Continuous attention to **technical excellence** and **good design**
10. **Simplicity** -*the art of maximizing the amount of work not done* – is essential
11. Best architectures, requirements, and designs emerge from **self-organizing teams**
12. Regularly, the team **reflects on how to become more effective**, and adjusts accordingly



Agile Manifesto

While there is value in the items on the right, we value the items on the left more.

Individuals and Interactions	Process and Tools
Scientific Discoveries	Comprehensive Documentation
Collaboration	Contract Negotiation
Responding to Change	Following a Plan



Risk



Credibility



Adaptability



Applicability



Knowledge

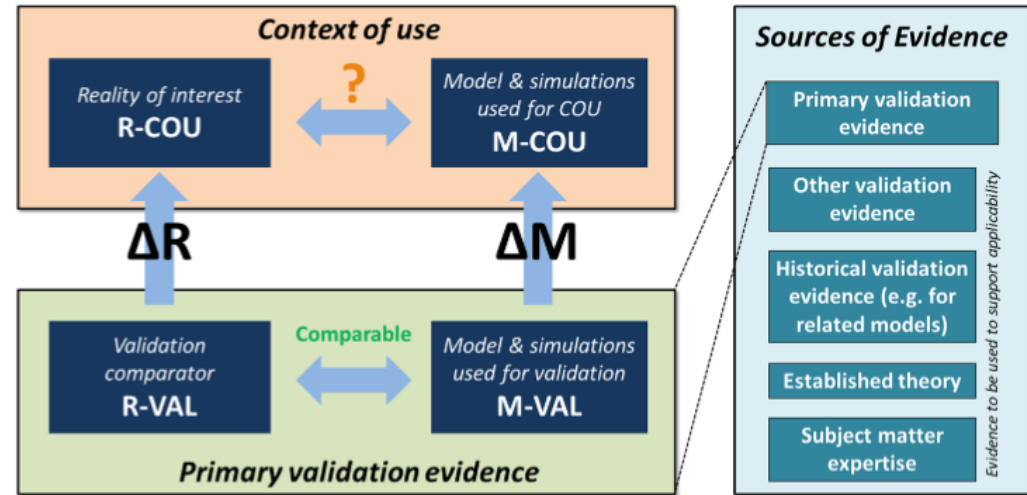


Project

Applicability Analysis

ABioM integrates

- Applicability Analysis
 - Planning
 - Final Analysis
- Define Domains
 - Context of Use (COU)
 - Validation
- Captures
 - Domain Differences
 - Limitations of the Computational Model



Pathmanathan et al. 2017: "Applicability Analysis of Validation Evidence for Biomedical Computational Model" ([Open Access](#))



Risk



Credibility



Adaptability



Applicability



Knowledge



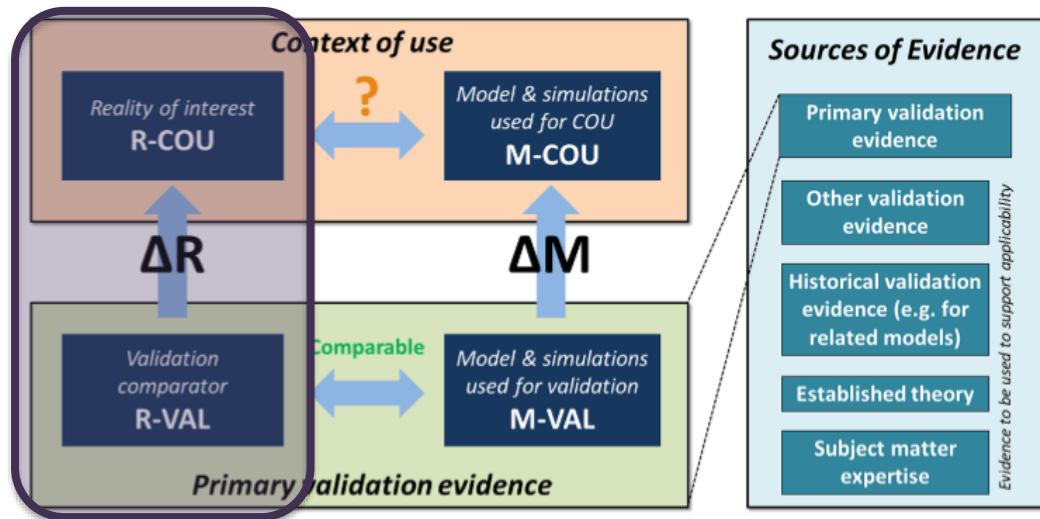
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Difference	R-VAL	R-COU



Pathmanathan et al. 2017: "Applicability Analysis of Validation Evidence for Biomedical Computational Model" (*Open Access*)



Risk



Credibility



Adaptability



Applicability



Knowledge

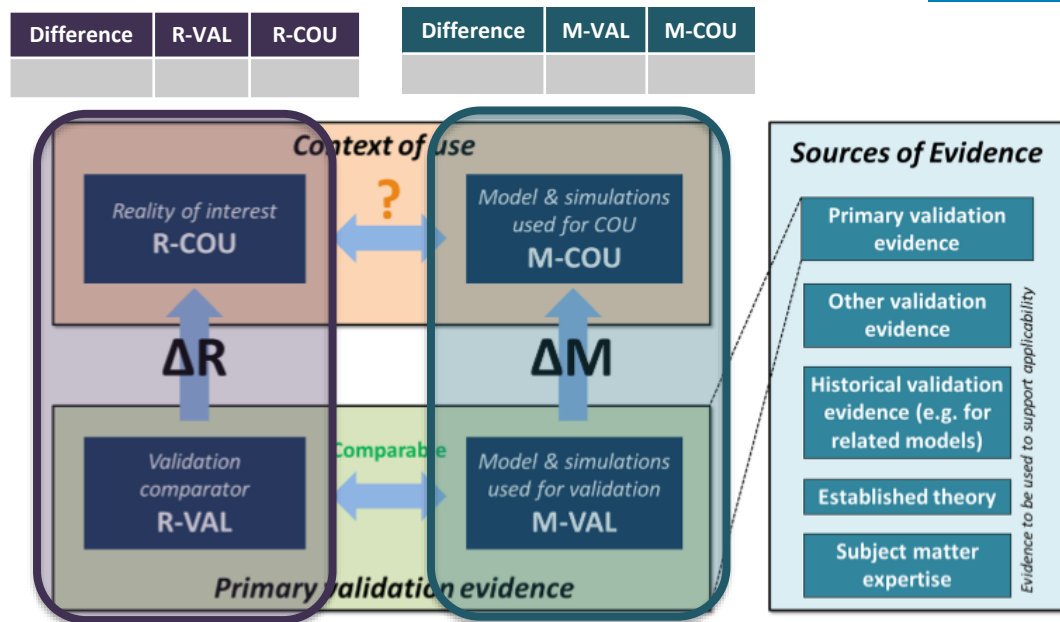


Project

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Risk



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Applicability



Knowledge



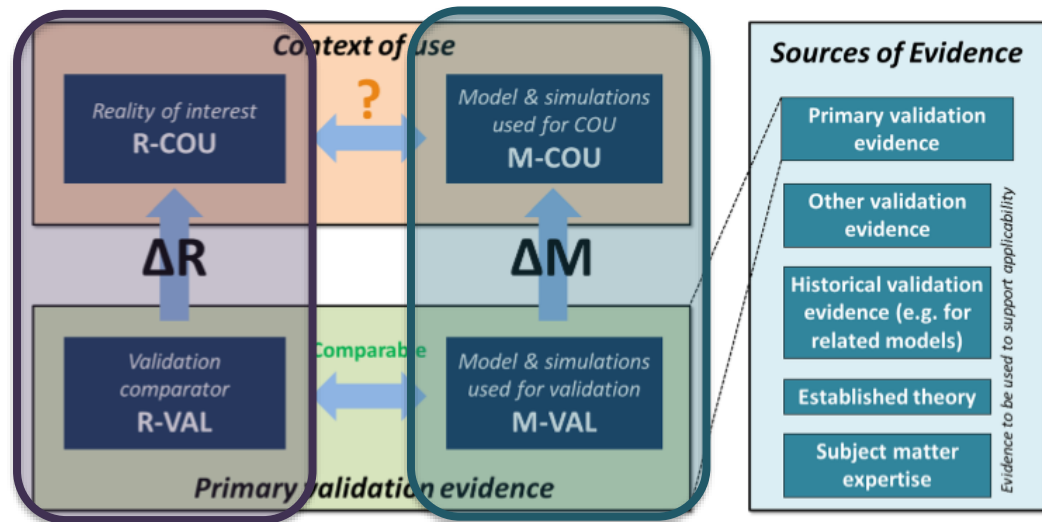
Project

Applicability Analysis

ABioM integrates

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Difference	R-VAL	R-COU	Difference	M-VAL	M-COU



Pathmanathan et al. 2017: "Applicability Analysis of Validation Evidence for Biomedical Computational Model" (*Open Access*)

Differences in Realities (R-Val and R-COU)	Similarities in Model (M-Val and M-COU)



Risk



Credibility



Adaptability



Applicability



Knowledge



Project

Knowledge Management

ABioM needs to main the state of knowledge and adapt as necessary:

- Ranking of Confidence and Knowledge of Interactions (ROCKIT)
 - Modified PIRT
- Difference between ROCKIT and PIRT
 - Ability to simulate system
 - Regarding All Phenomena
 - Experiments
 - Computational Model
 - Validation Systems
 - COU environments

Phenomenological Identification and Ranking Table (PIRT)

Phenomena	Importance	Confidence/Knowledge

Ranking of Confidence and Knowledge of Interactions (ROCKIT)

ROCKIT											Importance Scale: 1(most) to 3(low)
Type of Phenomena	Phenomena	Knowledge we have about what we're simulating	Our ability/knowledge to actually simulate it	Importance	Confidence in Importance	Confidence in Knowledge	How to Improve Confidence in Knowledge	VAL Domain	COU Domain	Notes	



Risk



Credibility



Adaptability



Applicability



Knowledge

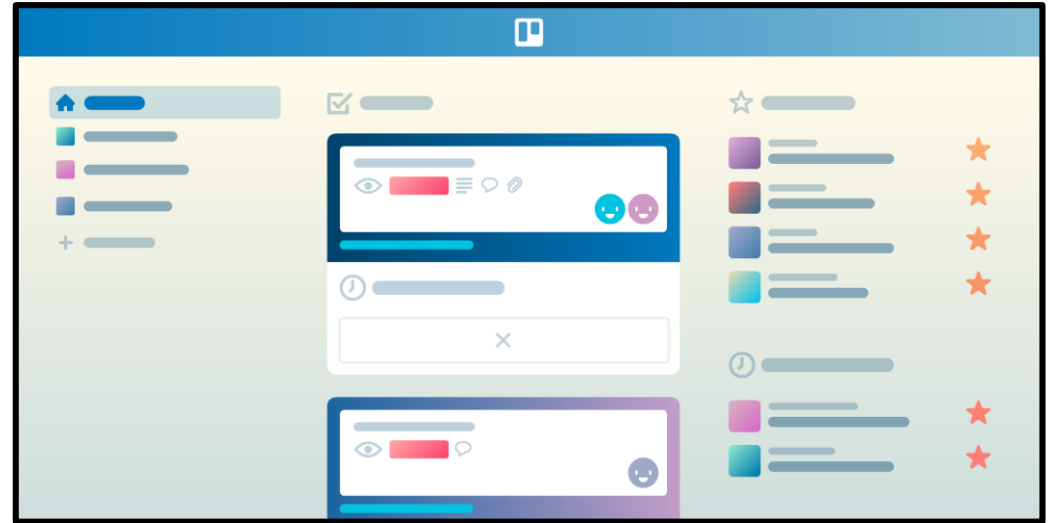


Project

Project Management

ABioM needs organization for all the moving parts:

- Project
 - Experiments
 - Computational Model
 - V&V Activities
- Team Members
- Resources
- Deadlines
- Decisions



Trello: <https://trello.com/>



Risk



Credibility



Adaptability



Applicability



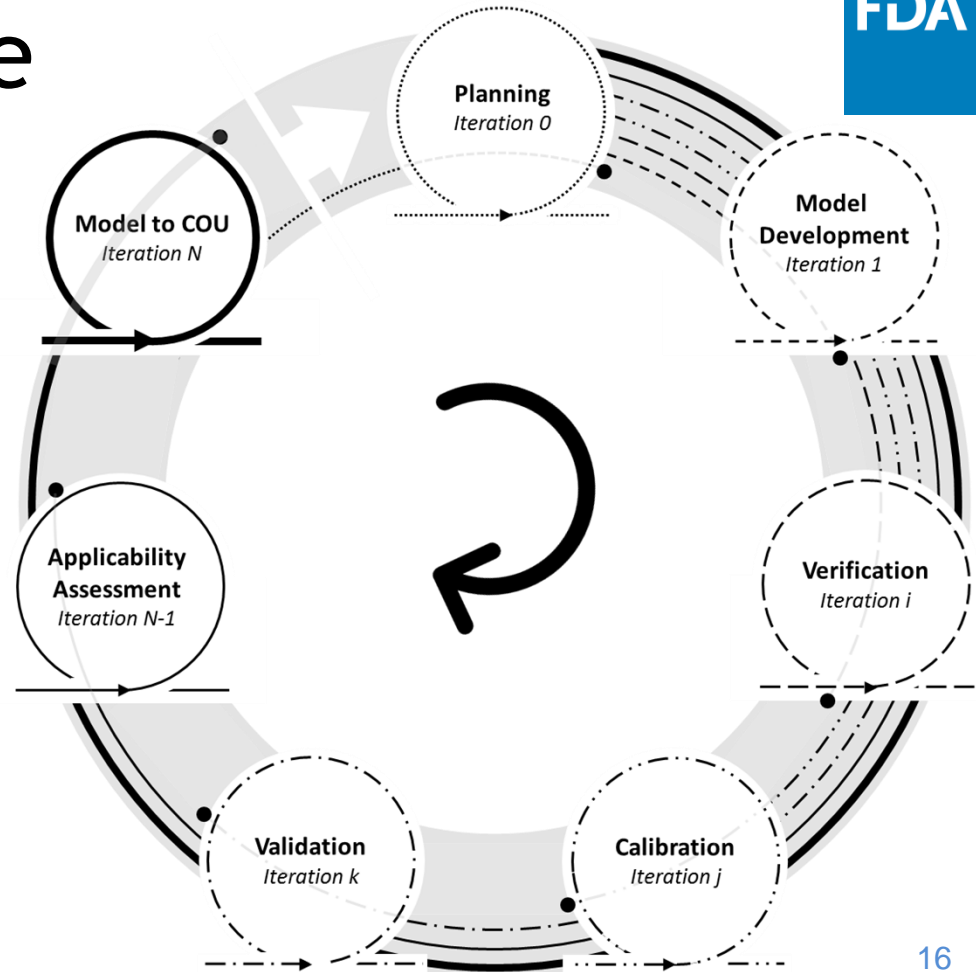
Knowledge



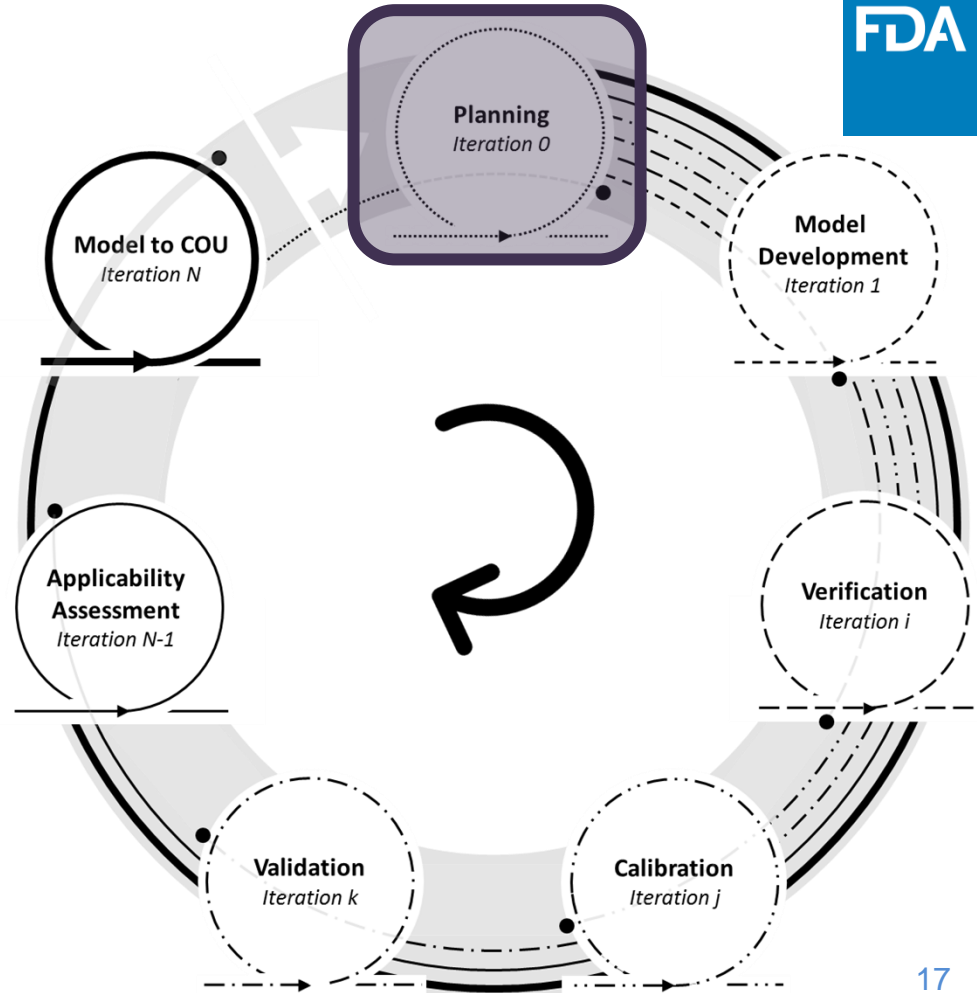
Project

ABioM Architecture

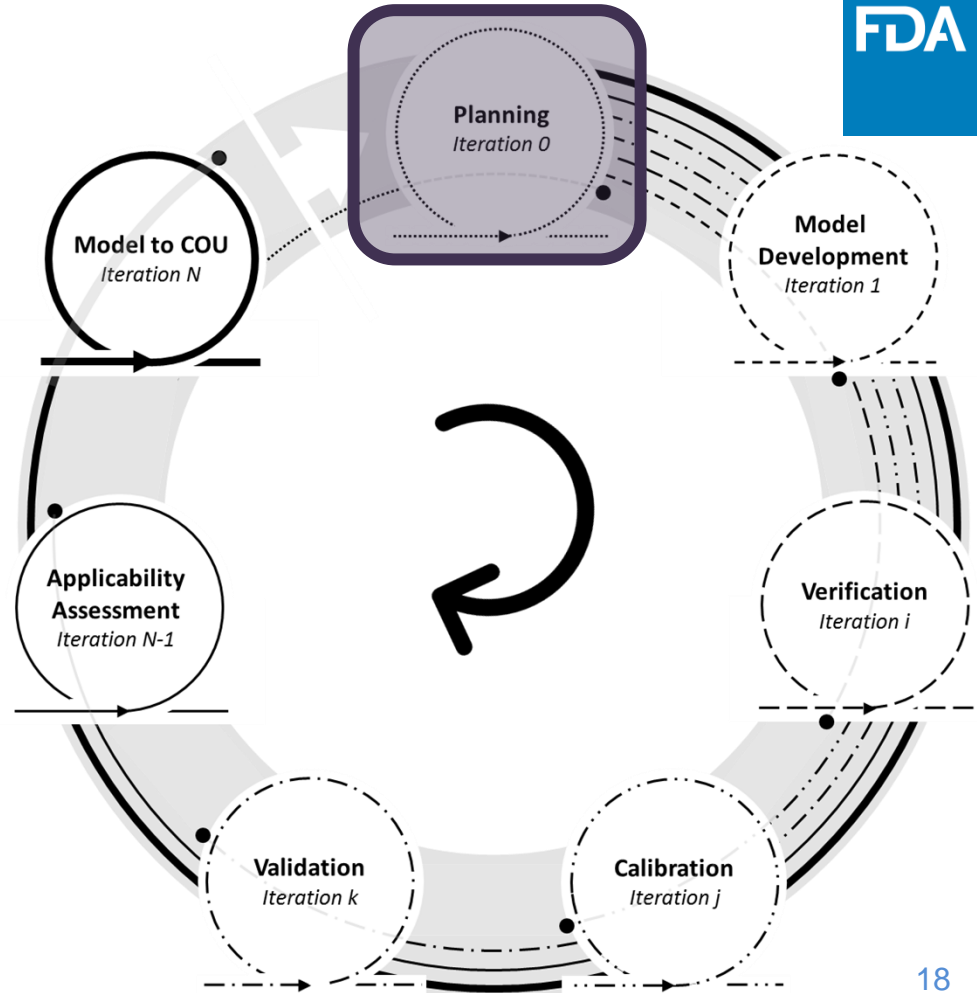
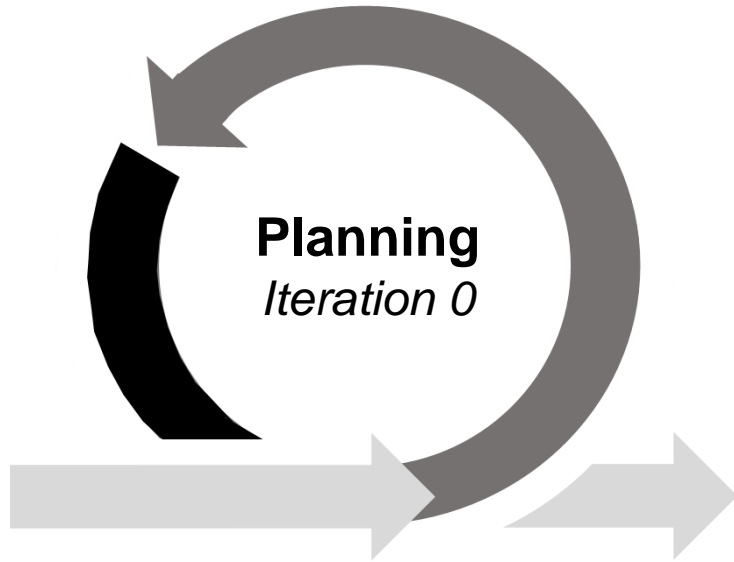
- Fundamental agile ideologies
- Adaptive decision making
- Iterative credibility building



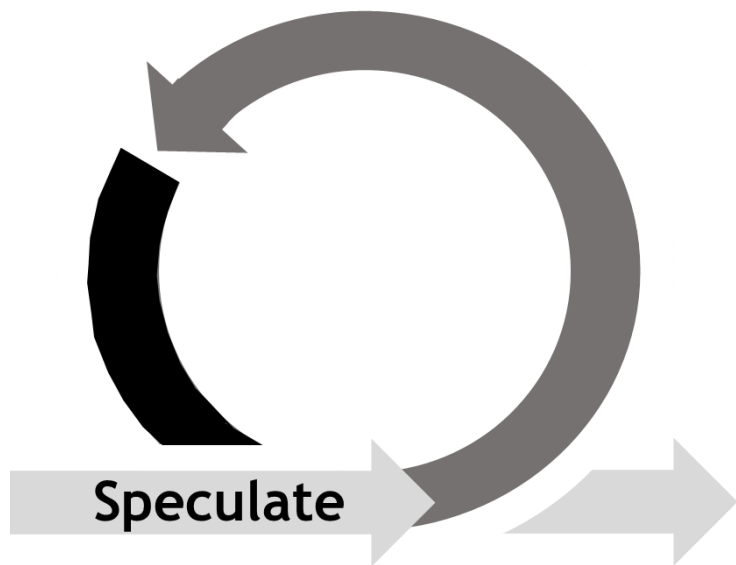
Single Iterations






Single Iterations

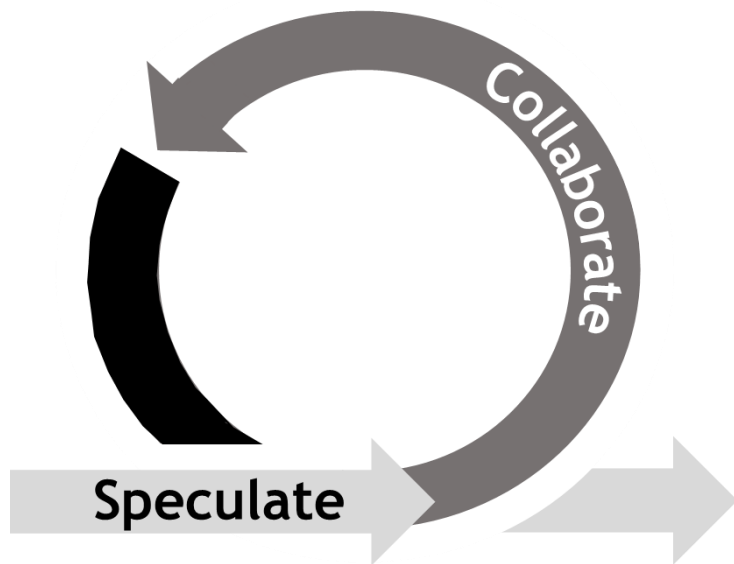



Single Iterations



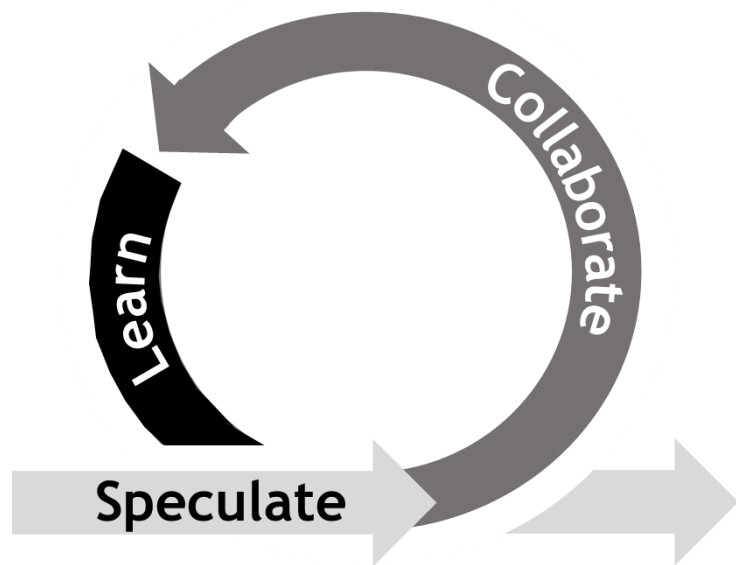
- **Speculate**
 - **Initial Requirements**
 - Initial 
 - Knowledge  
 - Backlog
- **Collaborate**
- **Learn**

Single Iterations



- **Speculate**
- **Collaborate**
 - **Develop**
 - Current Iteration
 - **Develop**
 - In Progress
 - **Quality Assurance** 
- **Learn**

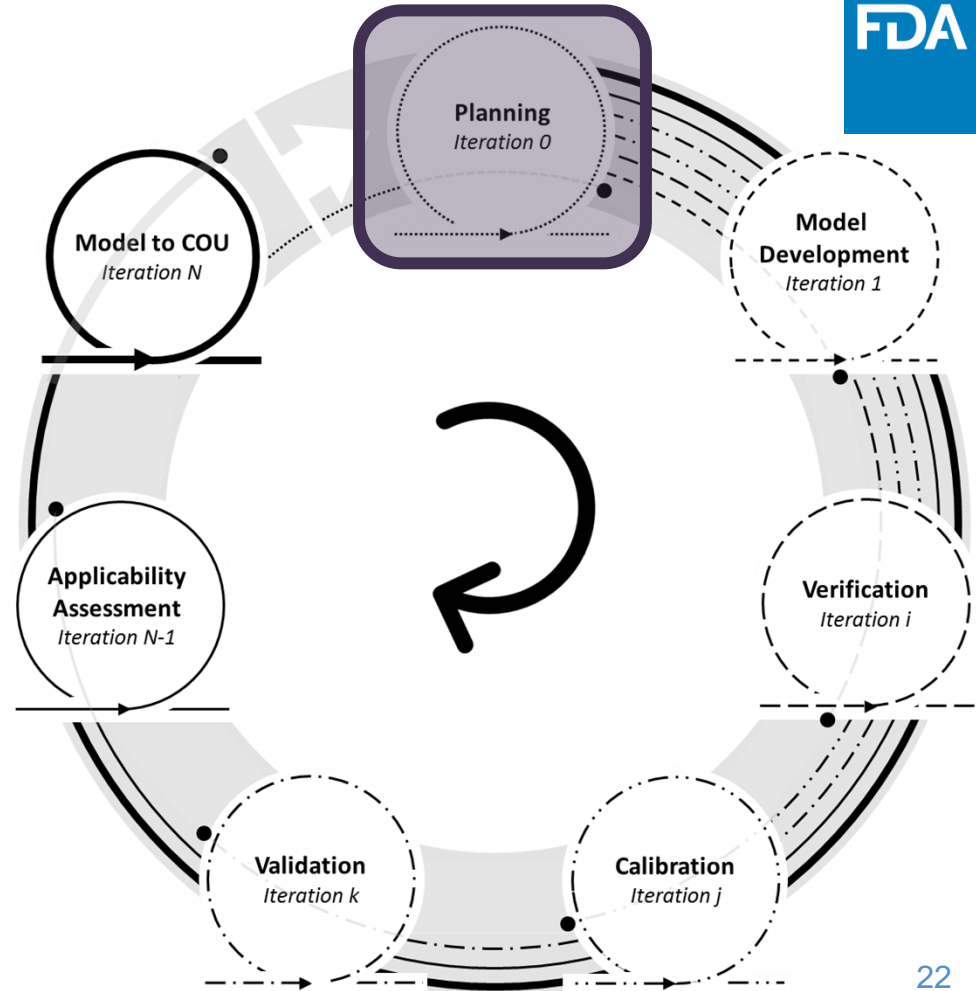
Single Iterations



- **Speculate**
- **Collaborate**
- **Learn**
 - **Review**
 - Completed Work
 - **Decision Making**

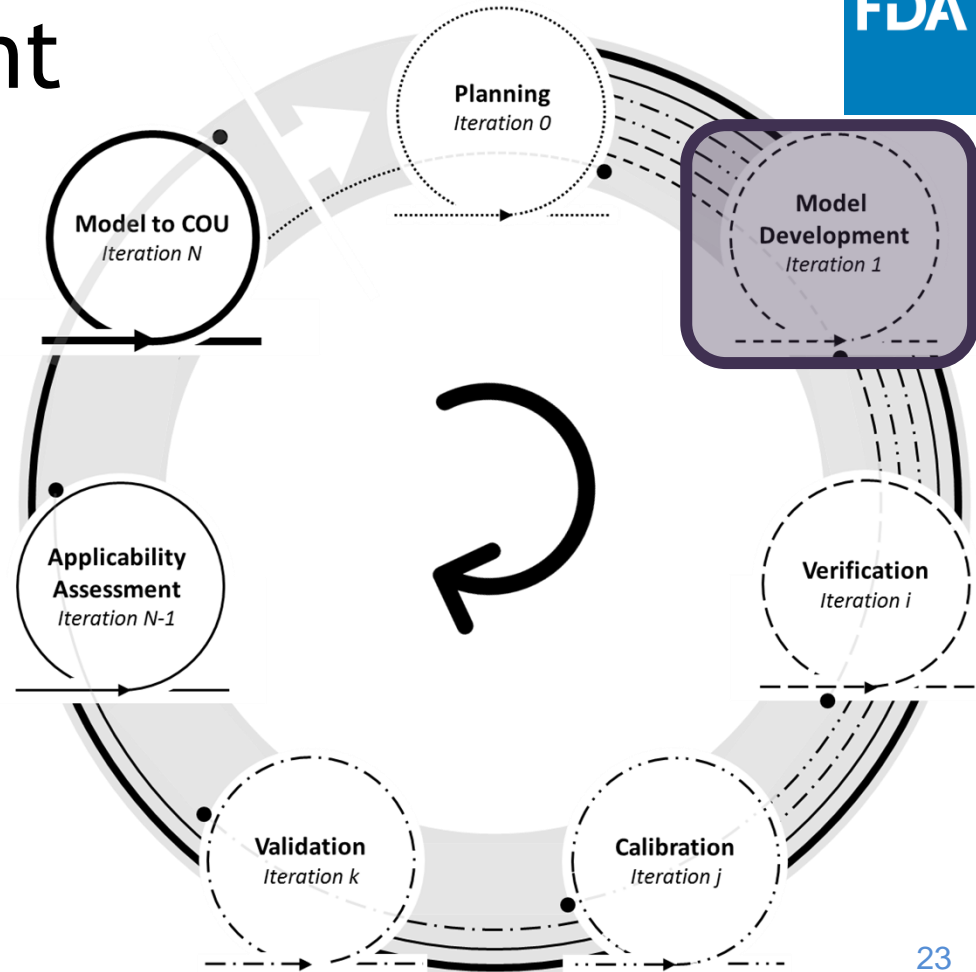
Planning

- Project Goals
 - Question of Interest
 - Context of Use
 - Risk Assessment
- Meeting Plan
- State of Knowledge
- Applicability Analysis Plan
- Iteration Plan



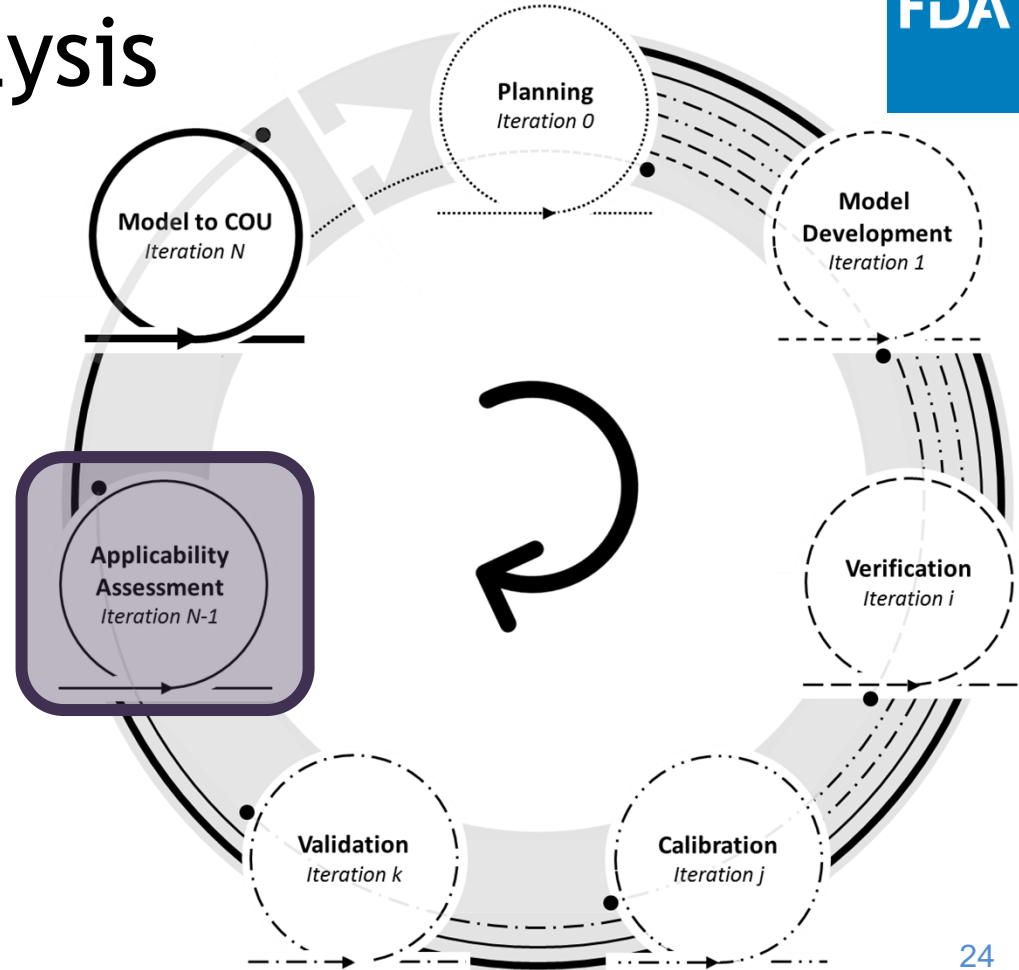
Model Development

- **Computational Model**
 - Re-use Computational Model
 - Limitations
 - Assumptions
 - Previous Context of Use
 - Previous Validation Efforts
 - New Computational Model
 - Complexity
 - Systems
- **Experiments:** Exploratory experiments
- **Other:** Investigate Applicability Assessment



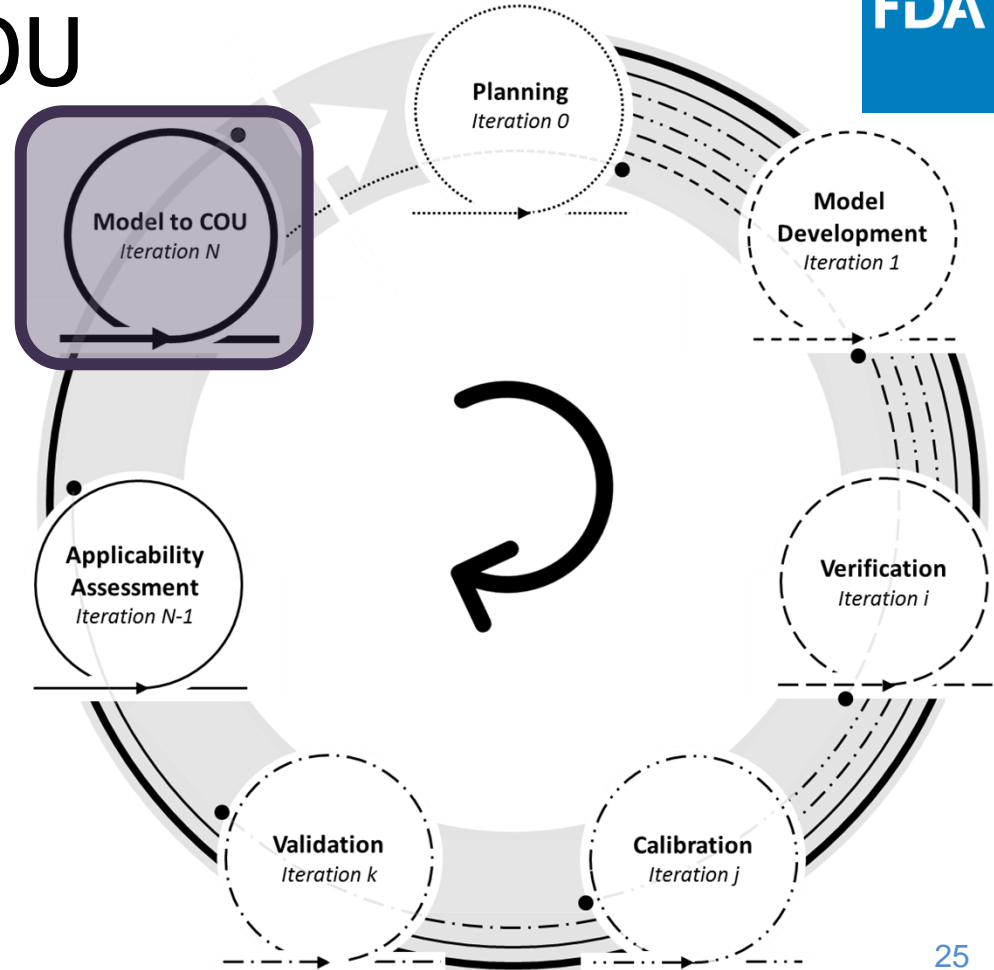
Applicability Analysis

- **Computational Model:** Conduct additional simulations for supplementary evidence
- **Experiments:** Conduct additional experiments for supplementary evidence
- **Other:** Complete investigating Applicability Assessment Concerns
- **Analysis**
 - Assess final Applicability Analysis
 - Assess all available evidence and justification
 - Determine if good enough to apply to the Context of Use
- Applicability Assessment

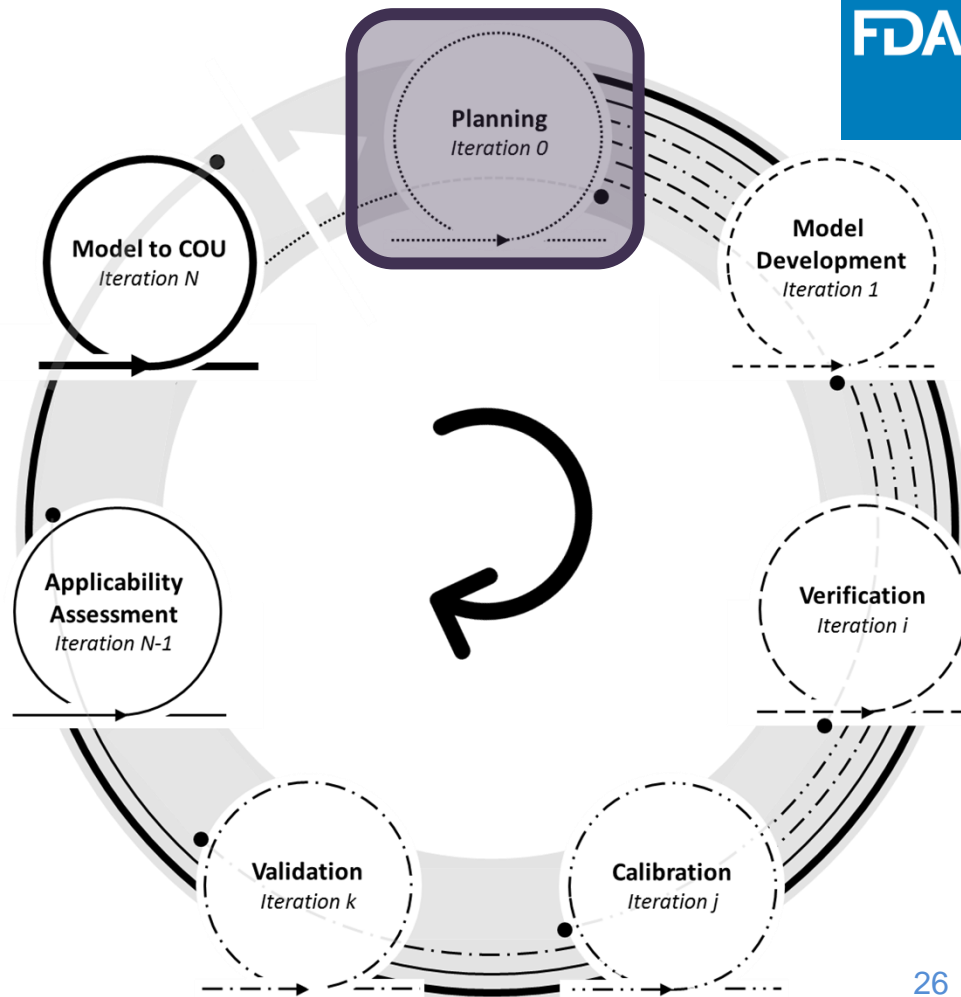
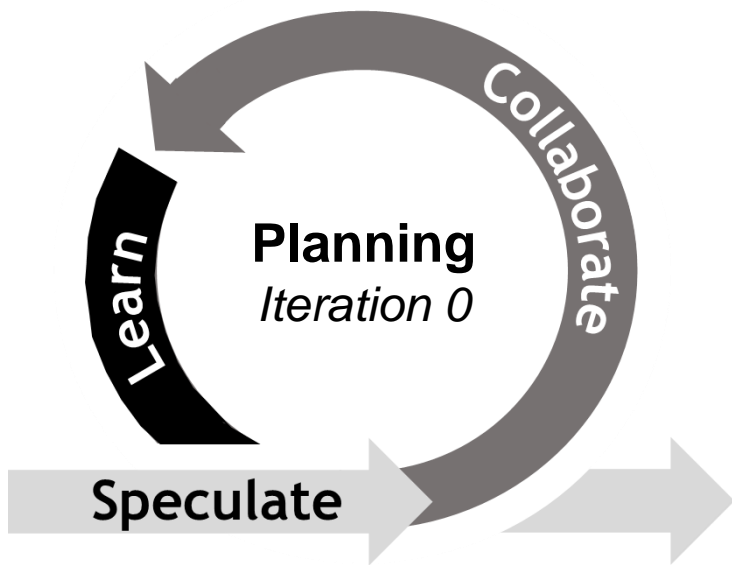


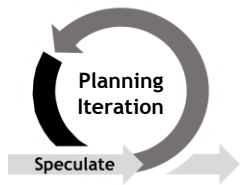
Apply Model to COU

- **Computational Model**
 - Modify for COU
 - Uncertainty Quantification (UQ)
 - Propagate new input parameters
 - Identify new uncertainties
 - Make final predictions
- **Experiments:**
 - Calibration experiments
 - Additional support
- **Analysis**
 - Address question of interest
 - Uncertainty Quantification Analysis for COU
 - Assess final predictions

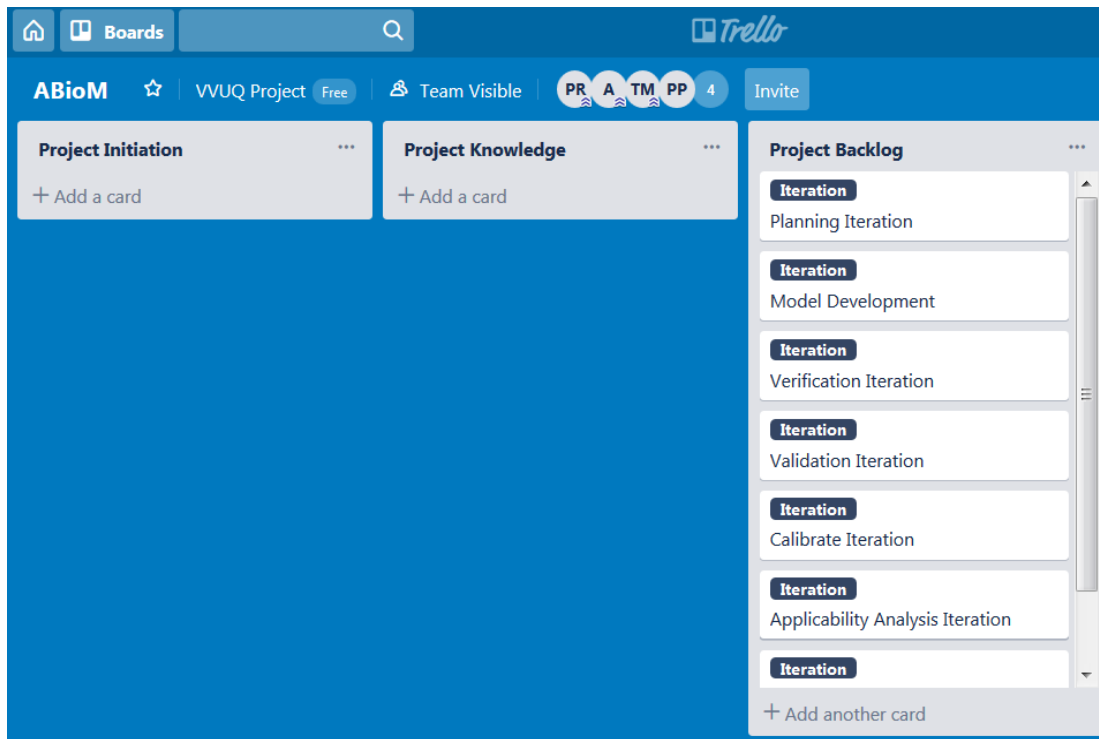


ABioM Demo

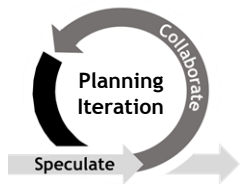




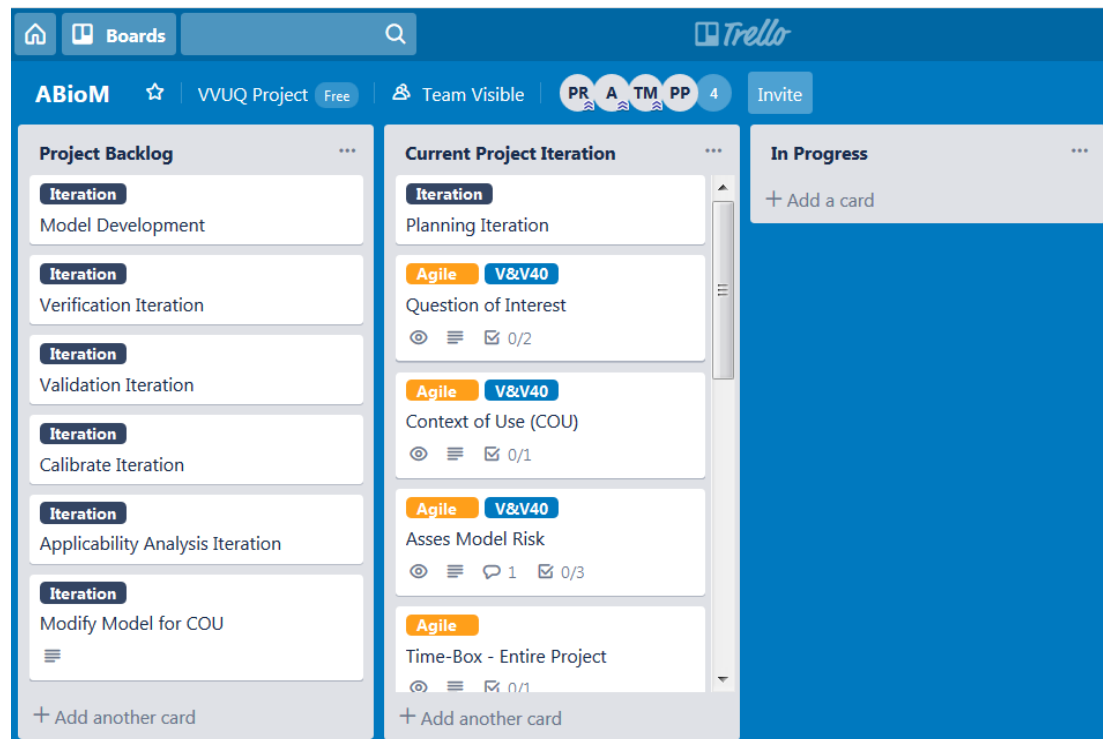
Requirements



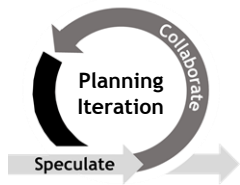
- Investigate & Establish
 - Project Initiation
 - Project Knowledge
 - Project Backlog
- For all 7 fundamental Iterations
- Different from other iterations



Develop

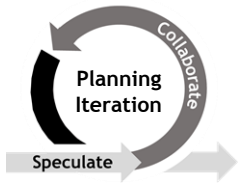


- **Current Iteration**
 - Choose Iteration
 - Determine tasks
- **In Progress**
- **Quality Assurance (QA)**

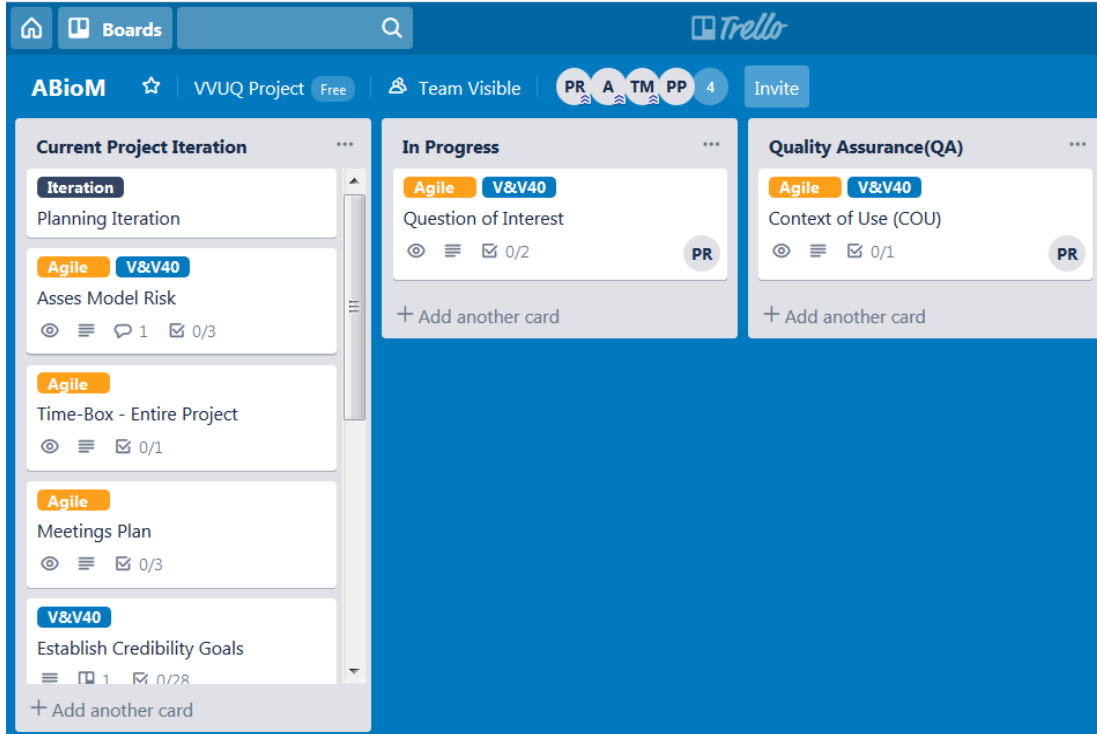


Develop

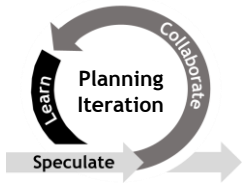
- **Current Iteration**
 - Choose Iteration
 - Determine tasks
- **In Progress**
 - Team members self assign tasks
- **Quality Assurance (QA)**



Quality Assurance (QA)

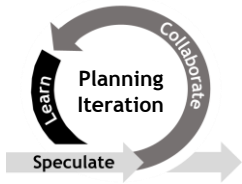


- **Current Iteration**
 - Choose Iteration
 - Determine tasks
- **In Progress**
 - Team members self assign tasks
- **QA**
 - Team members self assign tasks
 - Conduct additional work and analysis

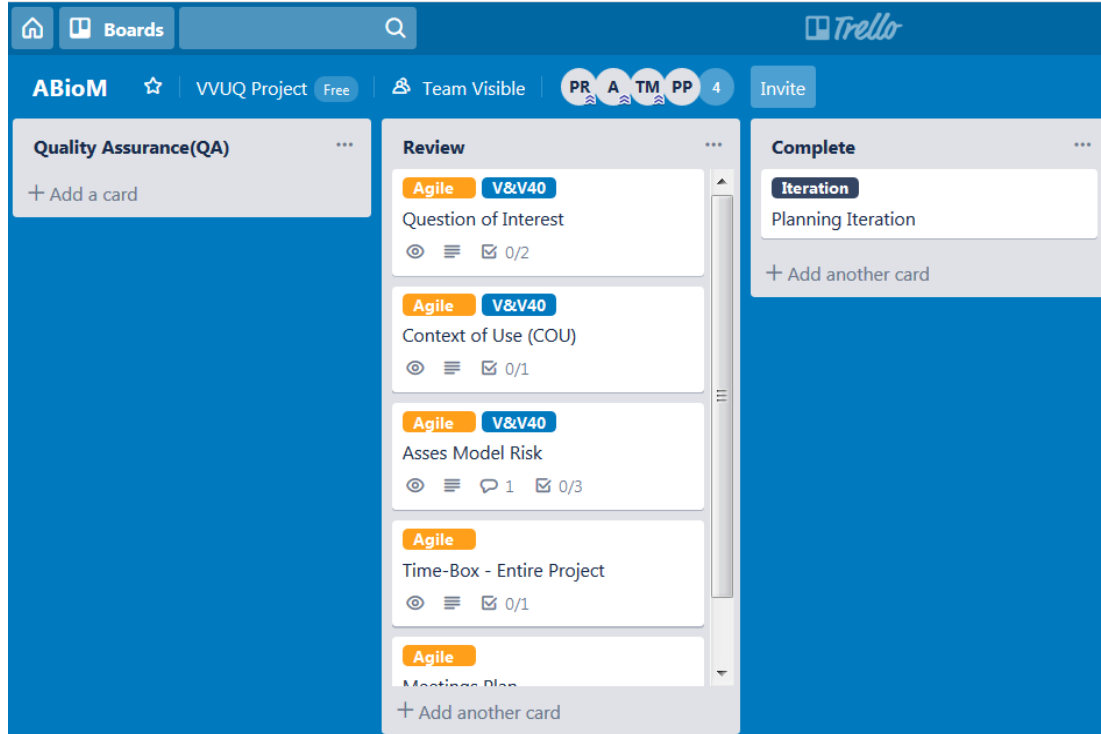


Review

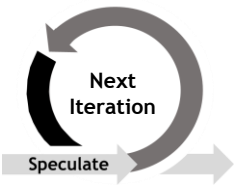
- Review efforts
 - Presentations
 - Reports
 - Data
 - Results
- Address additional concerns



Review



- Review efforts
 - Presentations
 - Reports
 - Data
 - Results
- Address additional concerns
- Assign to complete

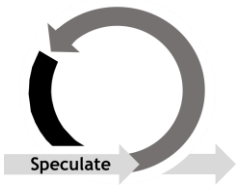


Update Requirements

The screenshot shows a Jira project board for 'V&V40'. The board is organized into three main columns:

- Project Initiation:** Contains cards for 'Question of Interest', 'Context of Use (COU)', 'Asses Model Risk', 'Time-Box - Entire Project', and 'Meeting Plan'.
- Project Knowledge:** Contains a 'V&V40' card with a diagram titled 'Context of Use' and 'Sources of Evidence'. The diagram shows 'R-COU' and 'M-COU' with a question mark between them, and 'M-VE' and 'R-VE' with a 'Comparison' label. Below this are cards for 'Applicability Analysis Planning' and 'ROCKIT aka PIRT'.
- Project Backlog:** Contains an 'Iteration' card for 'Model Development', followed by 'Task' cards for 'Air Flow Analysis' and 'Heated Airflow Analysis', and 'Iteration' cards for 'Verification Iteration' and 'Validation Iteration'.

- Project Goals
- Meeting Plan
- Credibility Goals
- ROCKIT
- Applicability Analysis Plan
- Iteration Plan



EDDS Project Initiation

Question of Interest

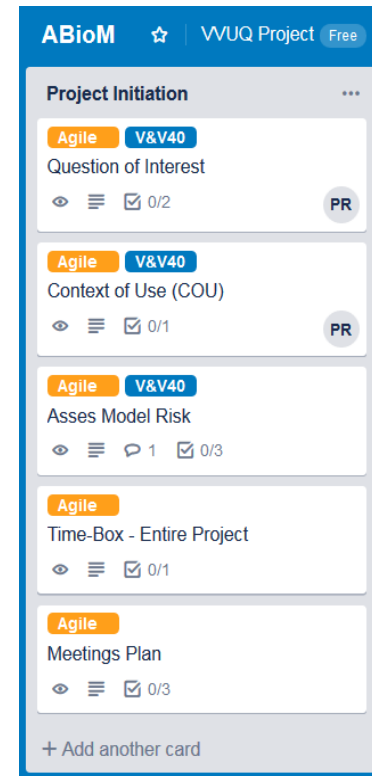
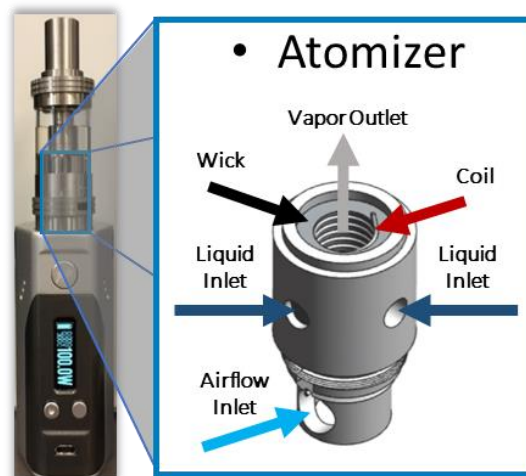
What are the bioeffects arising from deposition of potential chemicals generated by EDDS onto the oral mucosa?

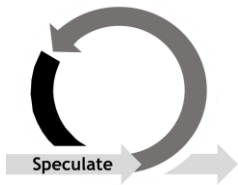
Context of Use

The computational fluid dynamics model will characterize the velocity field and temperature distribution of the flow in a representative mouth cavity of an EDDS user.

Model Risk

Model Risk: There is a *modest* possibility that the use of the computational model leads to a decision that results in patient harm and/or other undesirable impacts.



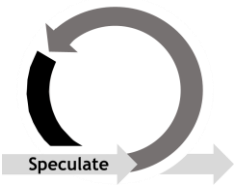


EDDS Knowledge

- Credibility Goals
- Based On:
 - Question of Interest
 - Context of Use
 - Model Risk

The screenshot displays a dashboard titled "Credibility Goals - Current Project". The dashboard includes a navigation bar with project details: "WVUQ Project", "Free", "Team Visible", and a notification bell with "6" items. Below the navigation bar, there are six goal cards, each with a title, a list of items, and a progress indicator.

Goal Category	Item	Progress
Verification: Code	Software Quality Assurance(SQA)	2/3
	Numerical Code Verification(NCV)	3/4
Verification: Calculation	Discretization Error	1/3
	Numerical Solver Error	1/3
Validation: Computational Model	Model Form	2/3
	Model Input - Quantification of Sensitivities	1/3
Validation: Comparator	Test Samples - Quantity	7/13
	Test Samples - Measurement	1/3
Validation: Assessment	Equivalency of Input Parameters	1/3
	Output Comparison - Quantity	1/2
Applicability	Step 1: Aim of the Computational Modeling	4/1
	Step 2: R-COU & M-COU	1/1



EDDS Knowledge



Test Samples - Quantity
in list *Validation: Comparator*

LABELS
Airflow +

Description Edit
I. Quantity of Test Samples: This component of the credibility factor examines the number of samples used in the comparator study. Increased credibility is generally achieved with a larger number of samples.

Gradation Hide completed items Delete
33%
 A single sample was used;
 Multiple samples were used, but not enough to be statistically relevant;
 A statistically relevant number of samples were used.

Add Comment
Write a comment... Save

ADD TO CARD
Members
Labels
Checklist
Due Date
Attachment

POWER-UPS
Get Power-Ups

ACTIONS
Move
Copy
Watch
Archive
Share

- Credibility Goals
- Based On:
 - Question of Interest
 - Context of Use
 - Model Risk

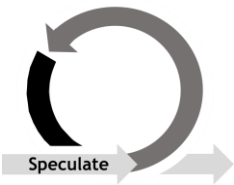
Credibility Goals

Verification: Code
Software Quality A
Numerical Code V
+ Add another card

Validation: Comparator
Test Samples - Quantity
Test Samples - Measurement
+ Add another card

Validation: Assessment
Equivalency of Input Parameters
Output Comparison - Quantity
+ Add another card

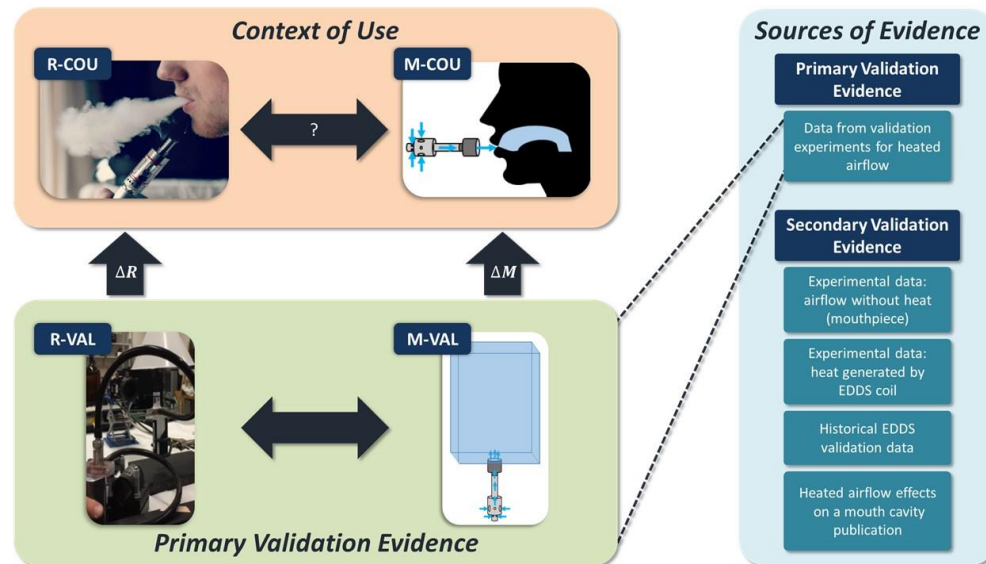
Applicability
Step 1: Aim of the Computational Modeling
Step 2: R-COU & M-COU
+ Add another card



EDDS Knowledge

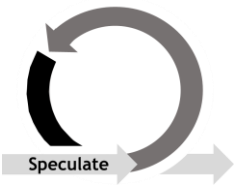


- Applicability Analysis Plan
- Define Domains:
 - Context of Use
 - Validation
- Sources of Evidence
- Quantities of Interest
- Assumptions & Limitations



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AA Step 8 Question: Can simulating only 3 airflow speeds, when in actuality the device can operate at any airflow speed, produce results that are not accurately representative of use therefore negatively impacting the study?



EDDS Knowledge



- Ranking of Confidence and Knowledge of Interactions Table (**ROCKIT**)
- VAL: Validation Domain
- COU: Context of Use Domain

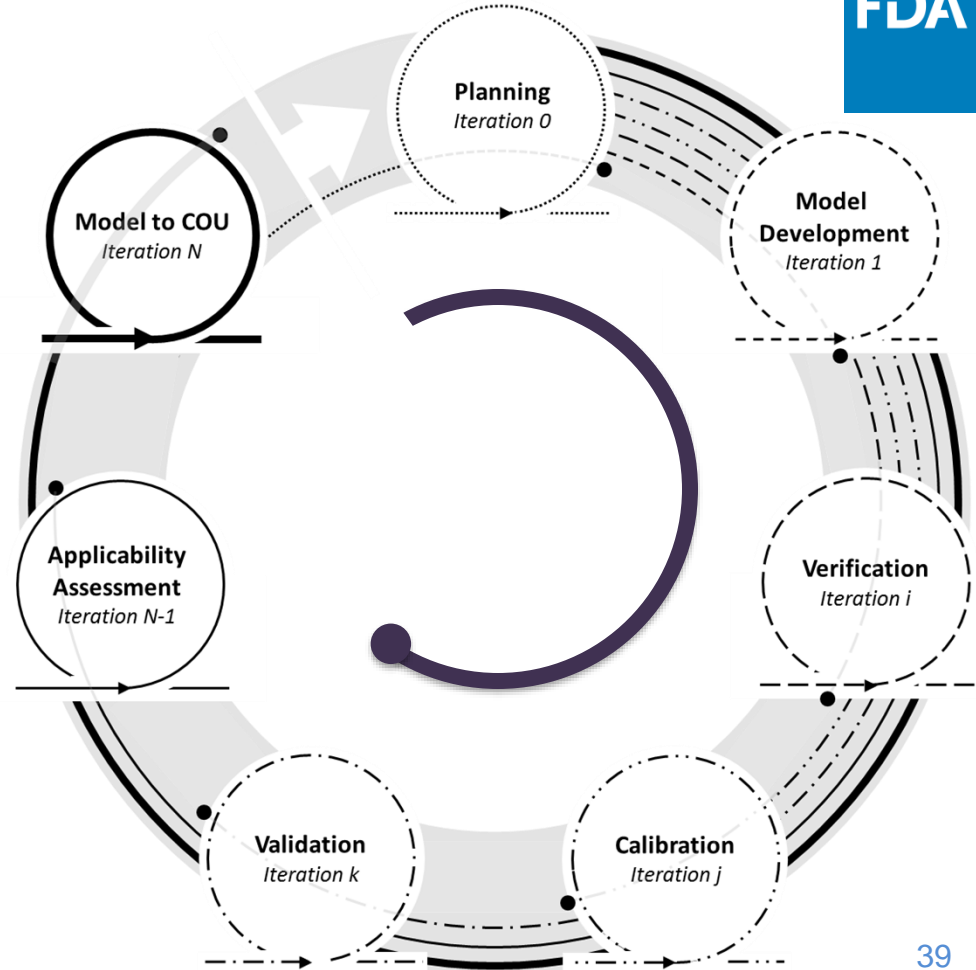
ROCKIT

Importance Scale: 1(most) to 3(least)
System: EDDS & mouthcavity

Type of Phenomena	Phenomena	Knowledge we have about what we're simulating	Our ability/knowledge to actually simulate it	Importance	Confidence in Importance	Confidence in Knowledge	How to Improve Confidence in Knowledge	VAL Domain	COU Domain	Notes
Input	Conservation of: * Mass * Momentum * Energy	Laws of Physics	Commercial software integrates laws	1	High	High	N/A	YES	YES	Commercial Software: ANSYS CFD- CFX
Output	Heated air temp. at the mouthpiece (Open Air)	Vapor temperature profile at the mouthpiece	* Commercial software integrates physics laws * Enter device geometry	1	High	High	N/A	YES	NO	Experiments: * Thermocouple measurements at the mouthpiece.
Output	Heated air temp. entering the mouth cavity	* Vapor temperature profile at the mouthpiece * Temp. in the mouth cavity (human temperature) * Mouth cavity configuration	* Commercial software integrates physics laws * Enter device geometry * Set mouth cavity boundary conditions	1	High	High	N/A	NO	YES	Output is a prediction in the COU domain Experiments: Not necessary
Input	Coil Temperature	Heating Coil Temperature/Heat Source	* Commercial software integrates physics laws * Enter coil geometry as heat source	1	High	High	N/A	YES	YES	Experiments: * Thermocouple measurements * Attach thermocouples to the coil using cement
Input	Ambient Temperature	Measurable	We can set the ambient temperature or consider a temperature difference	3	High	High	N/A	YES	YES	* VAL: We can consider a fixed laboratory Temp. * COU: This can be variable depending on usage
Output	Temperature through the EDDS	Large temperature variation	Simulate using commercial software	2	Medium	Low	Simulation & Experiments	YES	YES	Experiments: Thermocouple

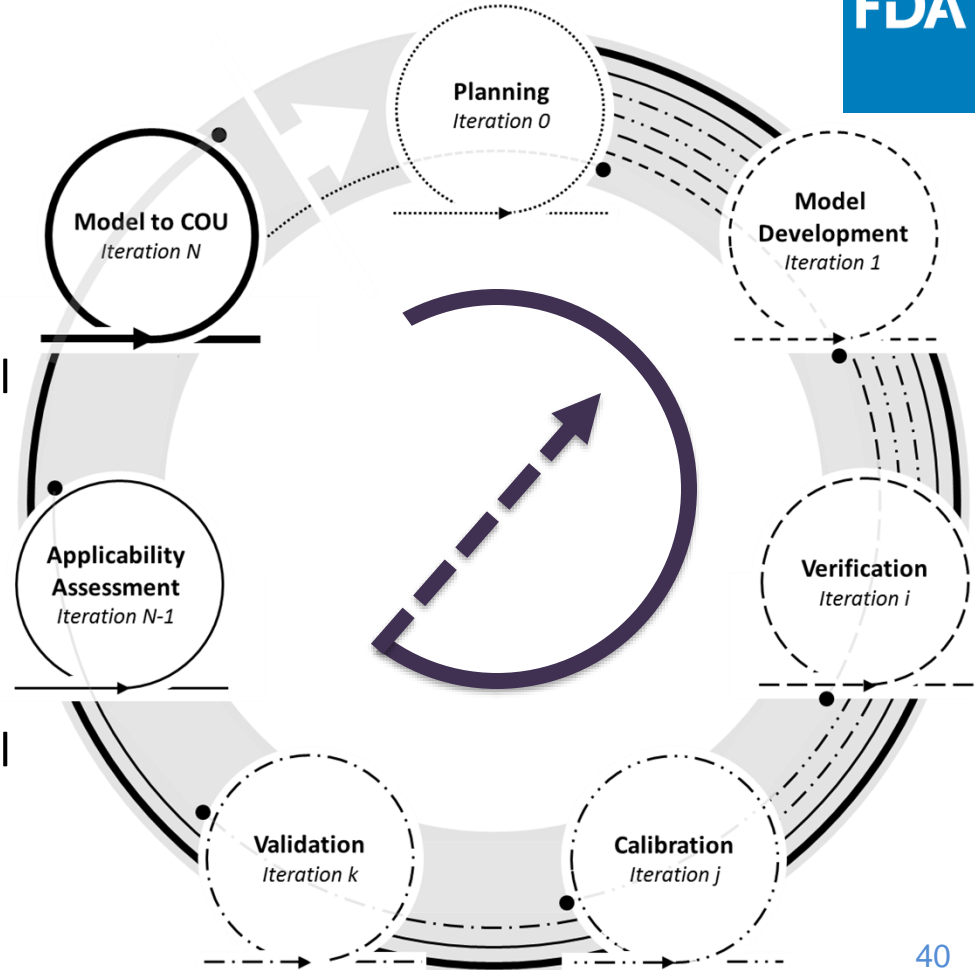
In Progress

- Current Iteration
 - Validation Iteration
 - Airflow only computational model (AFM 5.0)



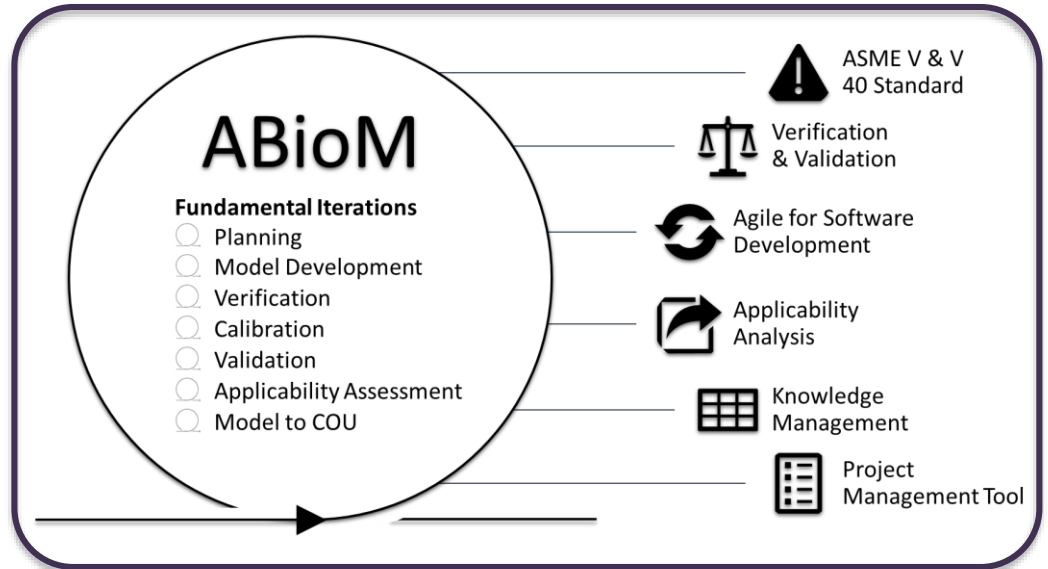
In Progress

- Current Iteration
 - Validation Iteration
 - Airflow only computational model (AFM 5.0)
- Next Iteration
 - Model Development Iteration
 - Airflow only computational model (AFM 6.0)
- Revisit Previous Iterations



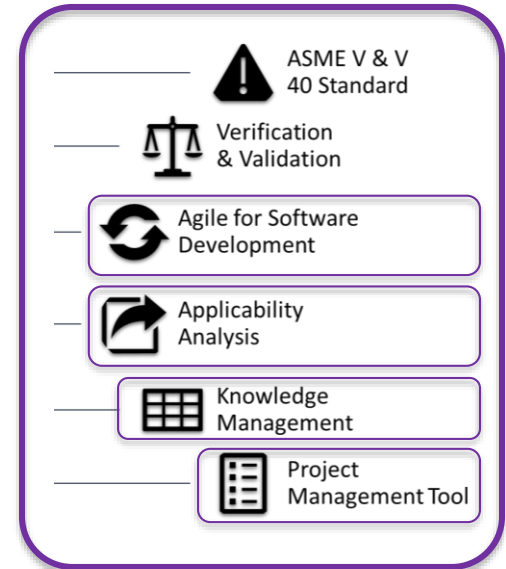
ABioM Summary

- Iterative Development
 - Credibility Building
 - V&V40 based QA
 - Applicability Analysis
 - Planning Iteration
 - Applicability Iteration
 - ROCKIT
- Interactive Collaboration
 - Communication
 - Assumptions
 - Limitations
 - Transparency
 - Informed decision making



ABioM Tools

- Manuscript in Progress
 - ABioM: An Agile Framework for Developing Credible Biomedical Models
 - Journal: Simulation Modelling Practice and Theory
 - Templates
 - Trello
 - ROCKIT
 - Applicability Analysis Plan
 - Iteration Plan
- Applicability Analysis Resources
 - Pathmanathan et al. 2017: “Applicability Analysis of Validation Evidence for Biomedical Computational Model” (**Open Access**)
 - Presentation by Dr. Morrison
 - Session: 10-2 VVUQ for Biomedical Engineering (**Thursday**)



Thank You.
Any Questions?

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