U.S. FOOD & DRUG ADMINISTRATION

An Agile Verification and Validation Process for Generating Regulatory-Grade Evidence

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Outline

- Motivation
- Agile Framework
- Modified Agile Approach
  - Integrated V&V40
- Project Management Tools
- Summary

Motivation

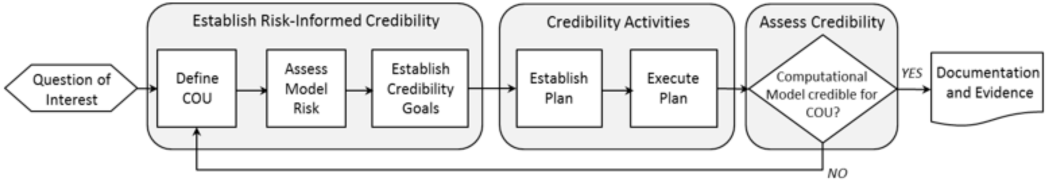
Some obstacles the medical device community faces in adopting computational models:

- Conducting sufficient verification and validation activities
- Implementing credibility assessment
- Identifying the necessary level of rigor
- Reporting activities implemented

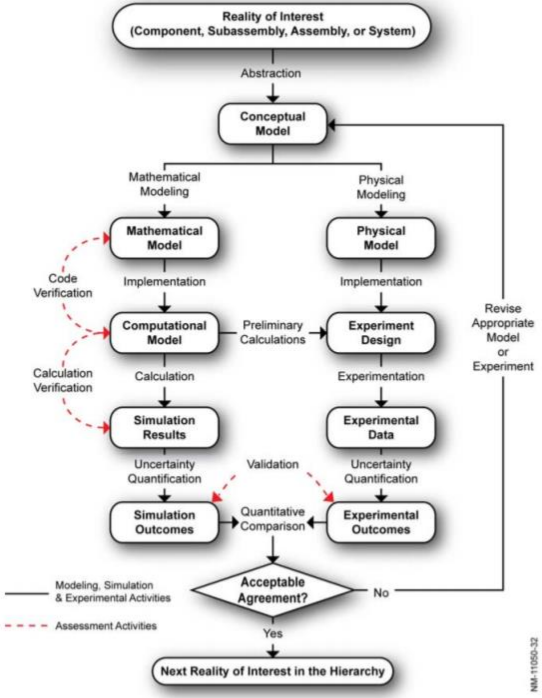
Goal: Execute an end-to-end example that utilizes risk-informed credibility assessment to produce a regulatory grade computational model for medical device evaluation.

Verification & Validation (V&V)

V&V40 - 2018 Standard



V&V10 - 2006 Standard

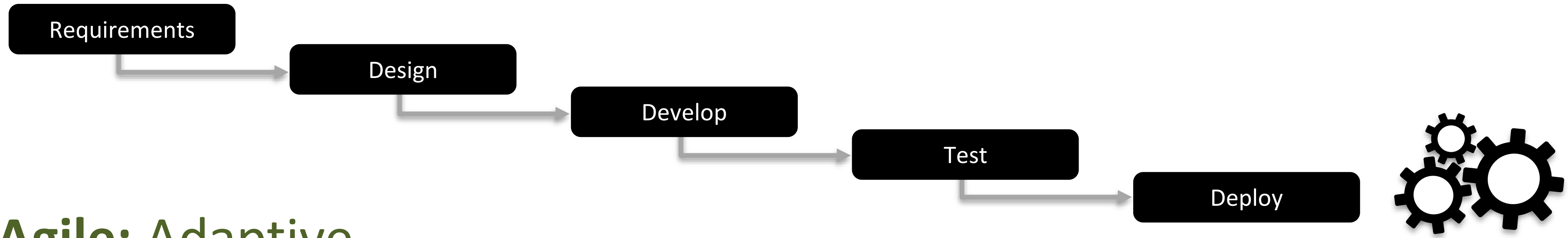


Agile Principles

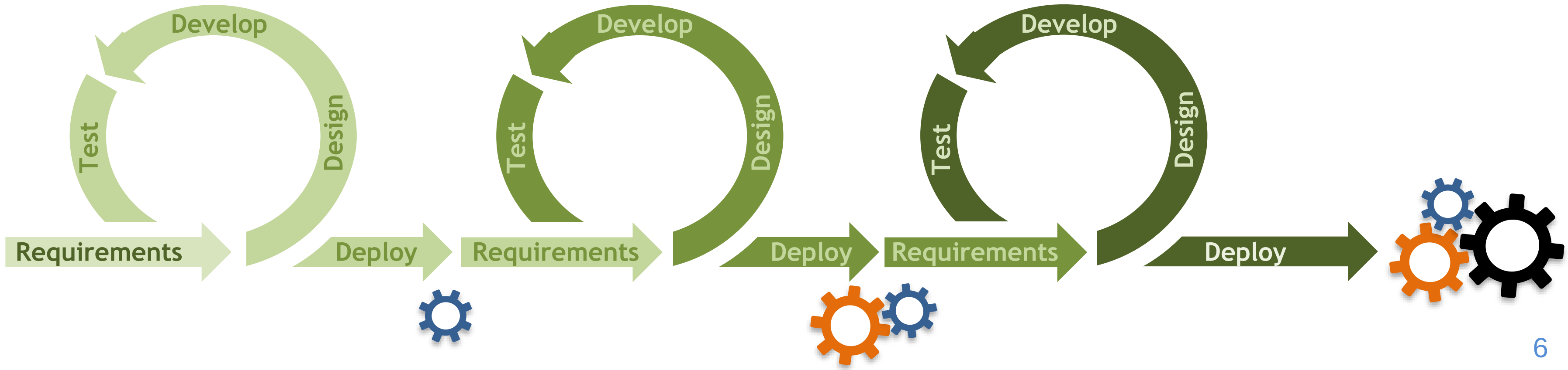
1. Early and **continuous** delivery of **valuable scientific discoveries**
2. Even in late development **welcome changing requirements**
3. Knowledge is **delivered frequently** (weeks rather than months)
4. Close, **daily cooperation** between researchers
5. Projects are built around **motivated individuals**, 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

Linear vs. Iterative Approach

Waterfall : Unidirectional



Agile: Adaptive

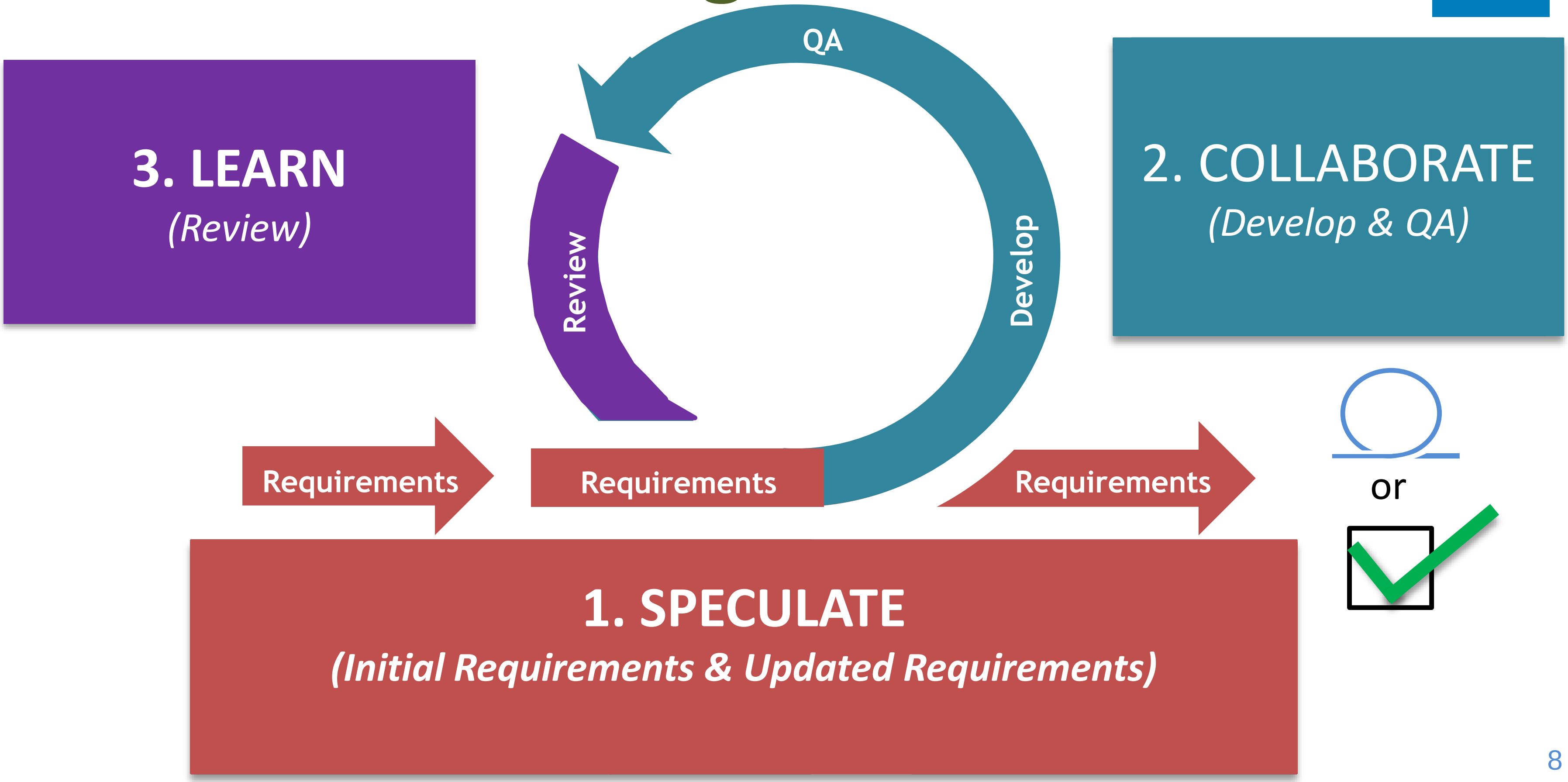


Agile Manifesto

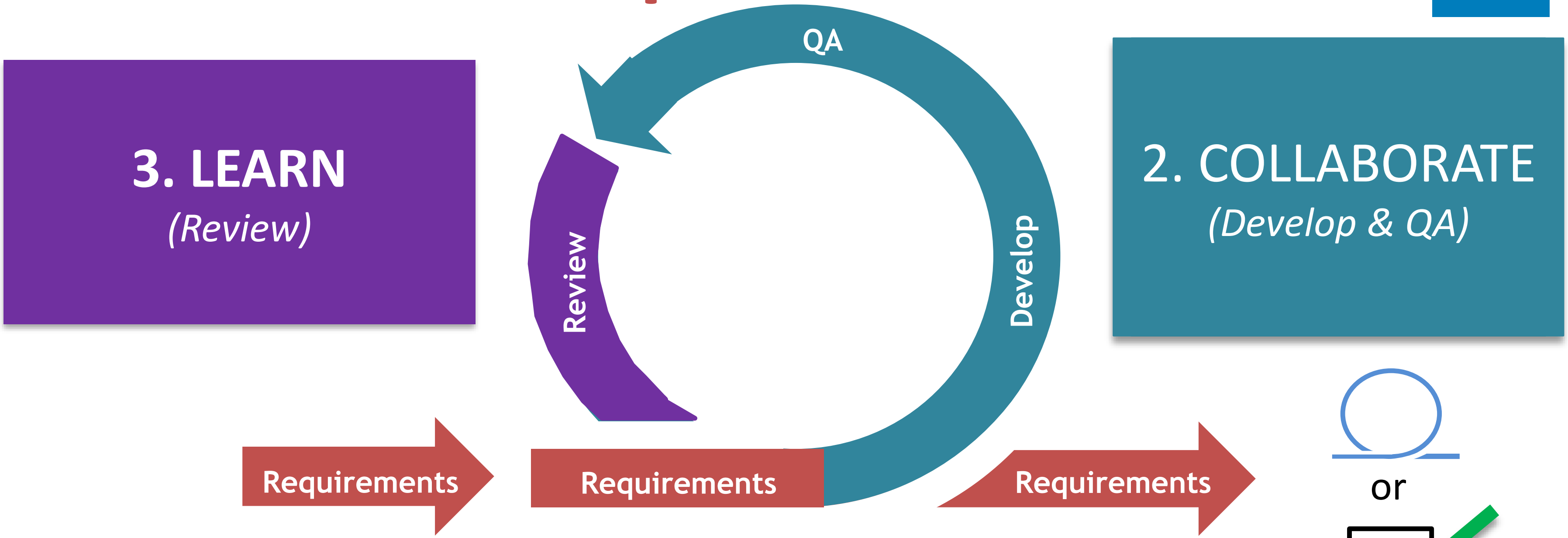
While there is value in the items on the right, we value the items on the left more.

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

Modified **Agile** Framework



Speculate



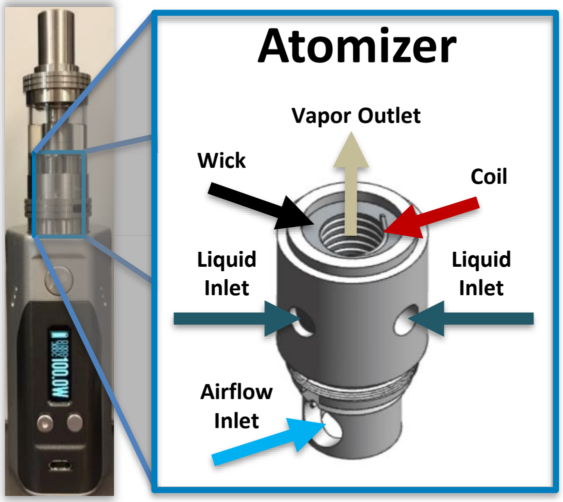
Initiation(I):	Knowledge(K):	Backlog(B):
- Question - COU - Model Risk - Time-box - Meetings	- Credibility Goals - PIRT - Plan iterations *(by complexity)* - Time-box	- List iterations in order (Trello)

4. SPECULATE
(Updated Requirements)

Speculate

Initiation(I):	Knowledge(K):	Backlog(B):
- Question	- **Credibility Goals**	- List iterations in order
- COU	- **PIRT**	(Trello)
- Model Risk	- Plan iterations	
- Time-box	*(by complexity)*	
- Meetings	- Time-box	

Photo by Jesus In Taiwan on Unsplash



Question of Interest

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

Context of Use (COU)

The CFD model will characterize the flow field and temperature distribution of the flow in 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.

Speculate

Initiation(I):	Knowledge(K):	Backlog(B):
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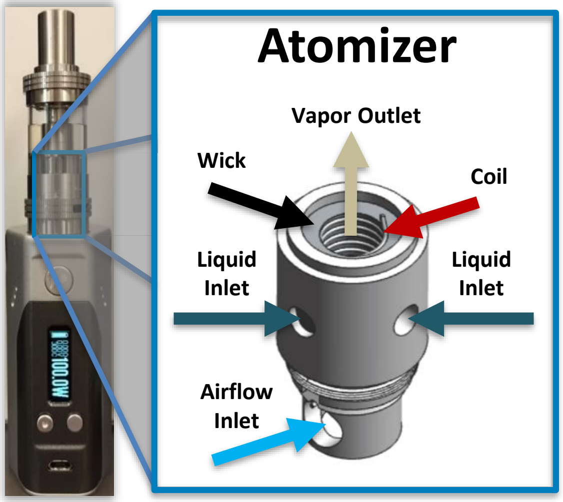

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Validation Domain → **COU Domain**

Speculate

Initiation(I):	**Knowledge(K):**	**Backlog(B):**
- **Question**	- **Credibility Factors**	- List iterations
- **COU**	- **PIRT**	in order
- **Model Risk**	- Plan iterations	(Trello)
- Time-box	*(by complexity)*	
- Meetings	- Time-box	

PIRT* – Version 1

(Phenomenological Identification and Ranking Table)

Phenomena	Importance	Confidence/Knowledge
Electral Power Input into heat		
Porosity		
Device Geometry		
Mixture of liquid		
Initial Temperature		
Ambient Temperature		
Pressure		
Air Flow Rate		
Average Air Velocity		

* Diamond, D. J. (2006), “Experience Using the Phenomena Identification and Ranking Technique for Nuclear Analysis,” BNL-76750-2006-CP, Brookhaven National Laboratory, Upton, NY

ASME V&V40 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 – Quantification of Sensitivities
  - Model Input – Quantification of Uncertainties
- Comparator (8 Factors)
  - Test Samples
  - Test Conditions
- Assessment
  - Equivalency of Input Parameters
  - Output Comparison – Quantity
  - Equivalency of Output Parameters
  - Rigor of Output Comparisons
  - Agreement of Output Comparisons

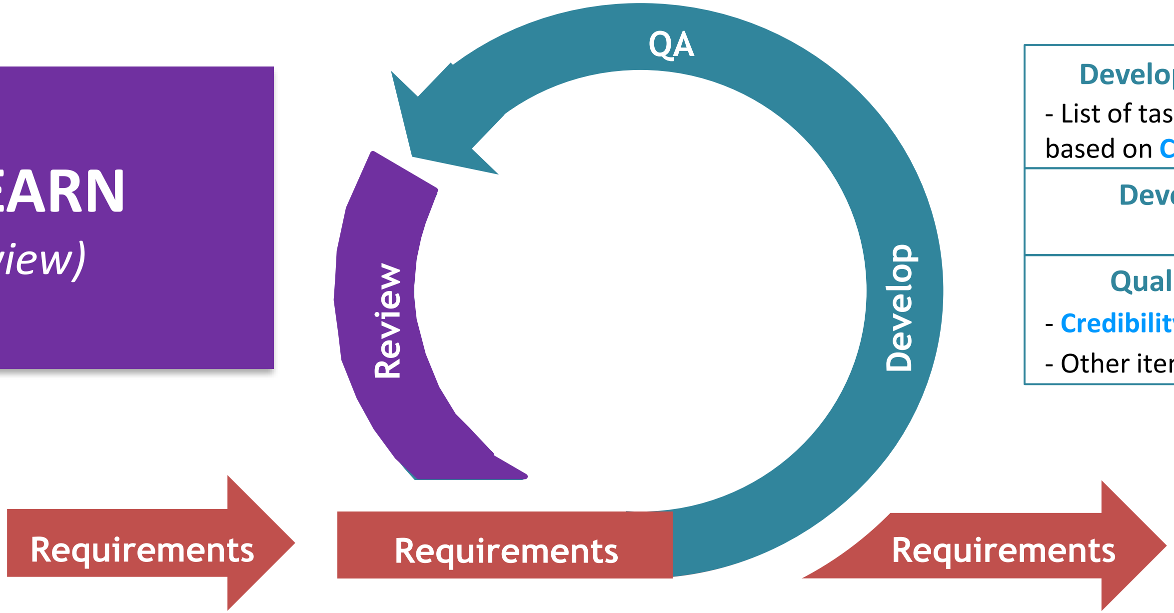
Applicability

- Relevance of the Quantities of Interest
- Relevance of the Validation Activities to the COU

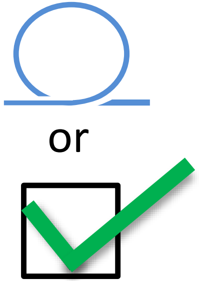
Collaborate

3. LEARN

(Review)



Develop – Current Iteration
- List of tasks to complete iteration based on **Credibility Goals** (Trello)
Develop – In Progress (Trello)
Quality Assurance(QA) - **Credibility Assessment** - Other items reviewed by team



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4. SPECULATE

(Updated Requirements)

Learn

Review:
- Meeting (Entire Team)
- Completed work is presented ***(demos)***
- **Did you compare the computational model with the comparator and is the assessment applicable for the COU?**

(Based on current evidence)

QA

Review

Develop

Develop – Current Iteration
- List of tasks to complete iteration based on **Credibility Goals** (Trello)
Develop – In Progress (Trello)
Quality Assurance(QA) - **Credibility Assessment** - Other items reviewed by team

Requirements → Requirements → Requirements

or

Initiation(I):	Knowledge(K):	Backlog(B):
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(Updated Requirements)

Speculate

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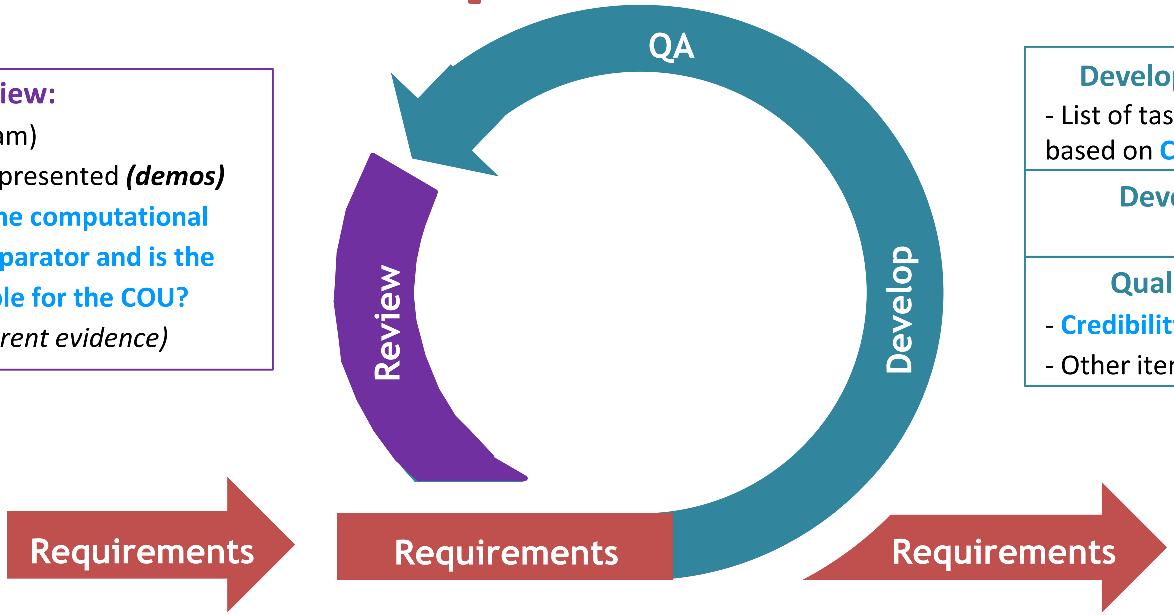

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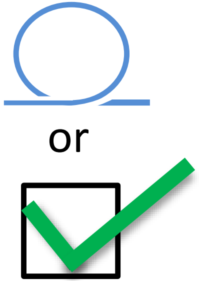
Develop – In Progress
(Trello)

Quality Assurance(QA)
- **Credibility Assessment**
- Other items reviewed by team



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- **Question** - **COU** - **Model Risk** - Time-box - Meetings	- **Credibility Goals** - **PIRT** - Plan iterations *(by complexity)* - Time-box	- List iterations in order (Trello)

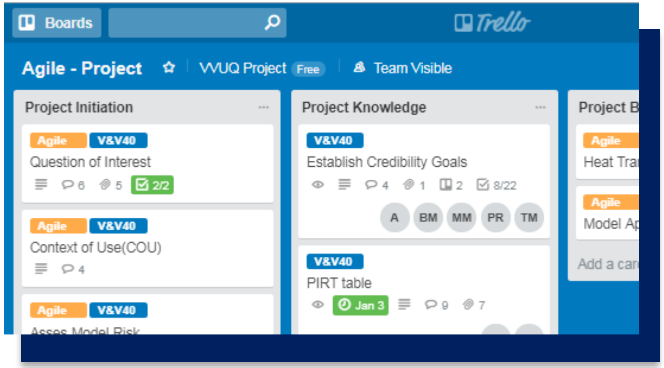
Proceed:
- Update **PIRT, Credibility Goals**
- If necessary, reorganize plan
- Begin next iteration

Tools

Trello*: *Web-Based Project Management Application*

Manages changes in:

- Project
- Team



PIRT**: *Phenomenological Identification and Ranking Table*

Monitors flux in knowledge:

- Expertise
- Experiments
- Literature Reviews

PIRT - Version 1

Phenomena	Importance	Confidence/Knowledge
Electral Power Input into heat		
Porosity		
Device Geometry		
Mixture of liquid		
Initial Temperature		
Ambient Temperature		
Pressure		

* *Commercial Software: https://trello.com/*

** *Diamond, D. J. (2006), "Experience Using the Phenomena Identification and Ranking Technique for Nuclear Analysis," BNL-76750-2006-CP, Brookhaven National Laboratory, Upton, NY*

Tools

PIRT - Version 6

Type of Phenomena	Phenomena	Importance	Confidence in Importance	Confidence in Knowledge	Knowledge we have about what we're simulating	Our ability/knowledge to actually simulate it	How to Improve Confidence in Knowledge	Notes
Input	Conservation of mass/momentum/energy	1	High	High	Laws are solid. No negotiation.	Laws already integrated in software.	N/A	ANSYS
Input	Mode of operation: constant power or constant temperature	1	Medium	High	high knowledge	Upload the measured power profile as the heat source. Note: Can be used for both modes even though the power profile is different.	N/A	constant power assumes constant heat source; constant temperature requires feedback Temperature Mode: (a) off: expect to have constant power output. (b) on: power varies to keep Temperature constant
Output	Temperature through out system	1	High	High	Air/smoke temperature profile	Physics Laws	Experiment for validation	Measured using thermocouples. At different locations inside the atomizer and mouthpiece.
		1	High	High	Heating Coil Temperature/Heat Source	Physics Laws	Experiment for validation	Measured using thermocouples Attach thermocouples to the coil using cement
Output	Nature of the air flow through the atomizer (tube) (assume it's laminar)	1	Medium	Low	mouthpiece particle velocity with PIV Note: May need to do some experiments to confirm Laminar Flow	CFD model of airflow only (NO Heat) to better characterize/understand airflow	Experiments using PIV	Based on Reynolds number calculation. **Single phase**: polystyrene beads **Dual phase**: smoke particles (if detectable in PIV)
Input	Airflow rate through cylinder (puff profile)	1	High	High	Measured airflow rate put into the system	airflow inlet boundary condition	N/A	Entire system, Velocity

PIRT - Version 1

Summary - Process

- Iteration
s

- PIRT

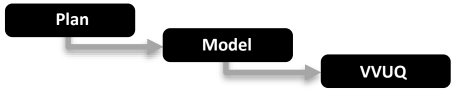
- Applicability Analysis*

* Based on “Applicability Analysis of Validation Evidence for Biomedical Computational Model” written by Pras Pathmanathan, Richard A. Gray, Vicente J. Romero, Tina M. Morrison, JVVUQ 2017 (***Open Access***)

Summary - Process

- Iterations
  - Start
    - Iteration Cycle 1

Waterfall



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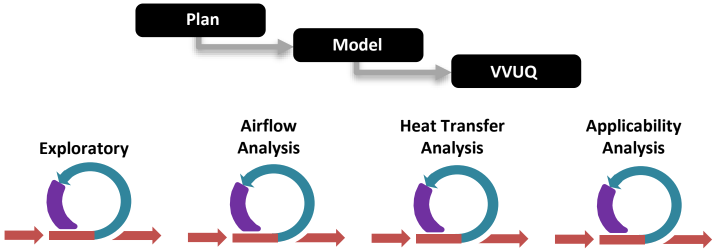
Summary - Process

- Iterations
  - Start
    - Iteration Cycle 1
  - Current
    - Iteration Cycle 2
- PIRT
- Applicability Analysis*

Waterfall

Agile



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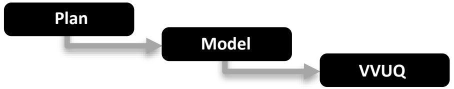
Summary - Process

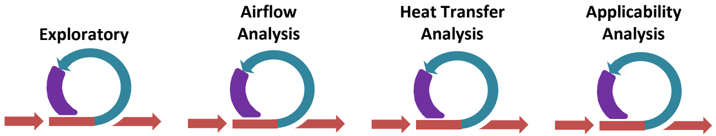
- Iterations
  - Start
    - Iteration Cycle 1
  - Current
    - Iteration Cycle 2
- PIRT
  - Start :
    - Version 1

- Applicability Analysis*

Waterfall



Agile



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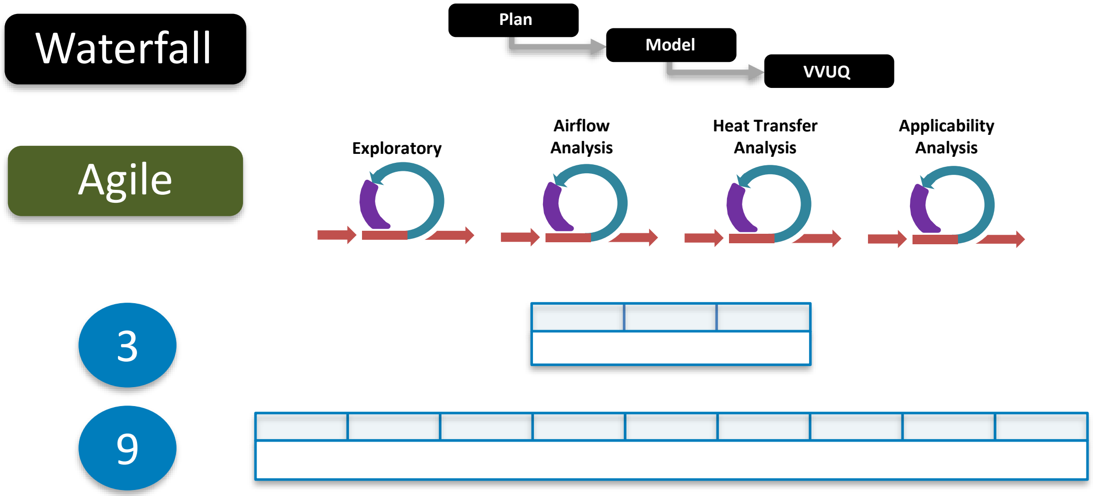
* Based on "Applicability Analysis of Validation Evidence for Biomedical Computational Model" written by Pras Pathmanathan, Richard A. Gray, Vicente J. Romero, Tina M. Morrison, JVVUQ 2017 (***Open Access***)

Summary - Process

- Iterations
  - Start
    - Iteration Cycle 1
  - Current
    - Iteration Cycle 2
- PIRT
  - Start :
    - Version 1
  - Current
    - Version 6
- Applicability Analysis*



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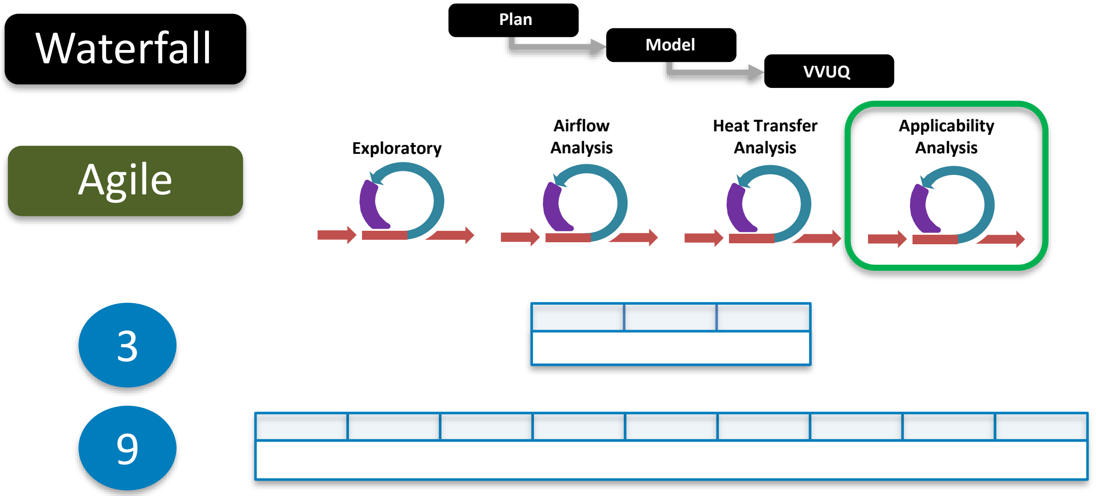
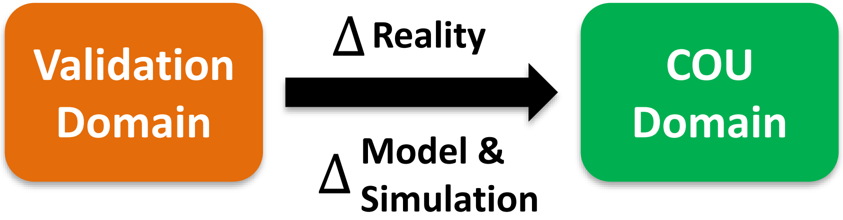
Summary - Process

- Iterations
  - Start
    - Iteration Cycle 1
  - Current
    - Iteration Cycle 2
- PIRT
  - Start
    - Version 1
  - Current
    - Version 6
- Applicability Analysis*
  - Required final iteration cycle
  - Interpolate or Extrapolate
  - Assess changes in Reality and Computational Model





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Summary - Implications

Enhance Communication

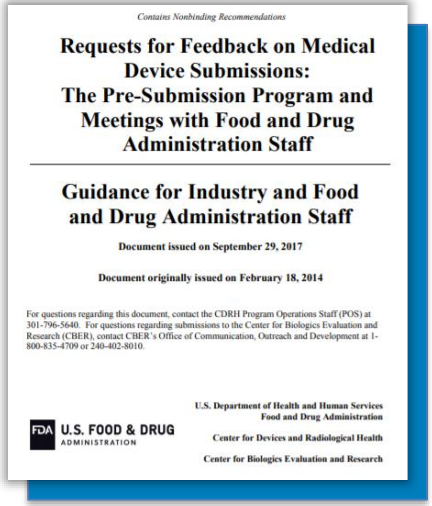
Cultivate Credible Models

Summary - Implications

Enhance Communication

- Team: Regulators, Modelers, & Experimentalists
- Facilitate early interactions between FDA and Industry
  - *Pre-Submission**

Cultivate Credible Models



Contains Nonbinding Recommendations

Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 29, 2017

Document originally issued on February 18, 2014

For questions regarding this document, contact the CDRH Program Operations Staff (POS) at 301-796-5640. For questions regarding submissions to the Center for Biologics Evaluation and Research (CBER), contact CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-8010.

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Food and Drug Administration

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* https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

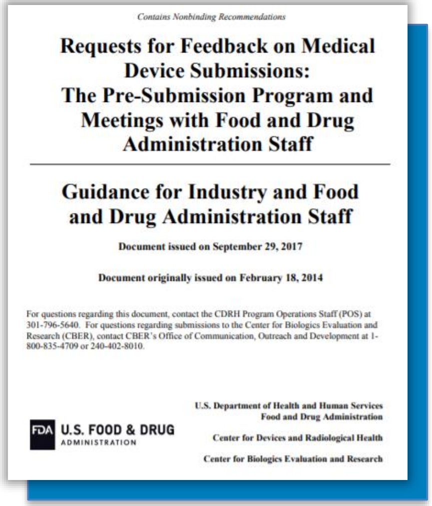
Summary - Implications

Enhance Communication

- Team: Regulators, Modelers, & Experimentalists
- Facilitate early interactions between FDA and Industry
  - ***Pre-Submission****

Cultivate Credible Models

- Adaptable framework that integrates the V&V40 Standard for a credible computational model dependent on a COU
- Iteratively builds credibility assessment into both the model and experiments during development and implementation
- Maintains consistency in expectations by following the **FDA Reporting of Computational Modeling Studies in Medical Devices Submissions Guidance****



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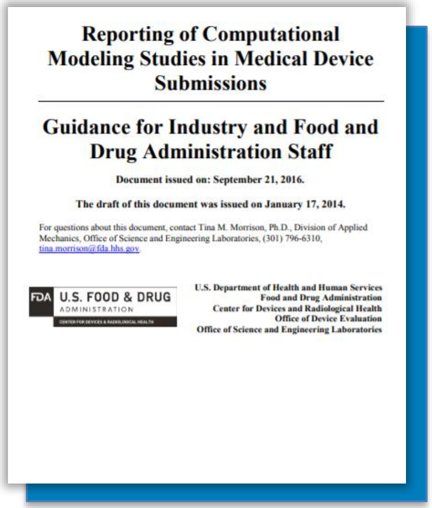

Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

The draft of this document was issued on January 17, 2014.

For questions about this document, contact Tina M. Morrison, Ph.D., Division of Applied Mechanics, Office of Science and Engineering Laboratories, (301) 796-6310, tina.morrison@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
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Office of Science and Engineering Laboratories

* https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

** https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381813.pdf

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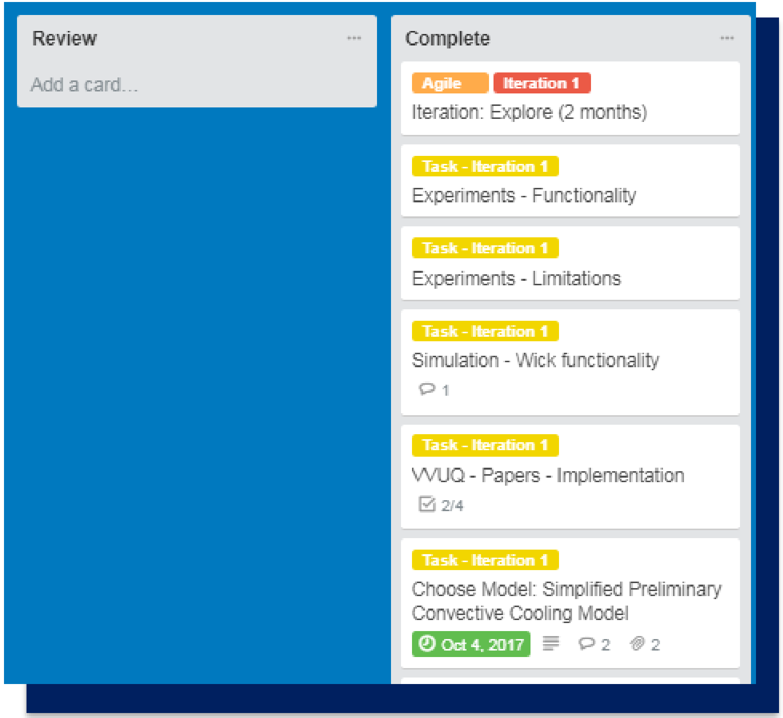
https://figshare.com/projects/Agile_V_V_Process/32072

ADDITIONAL SLIDES

Iteration – 1(*Completed*)

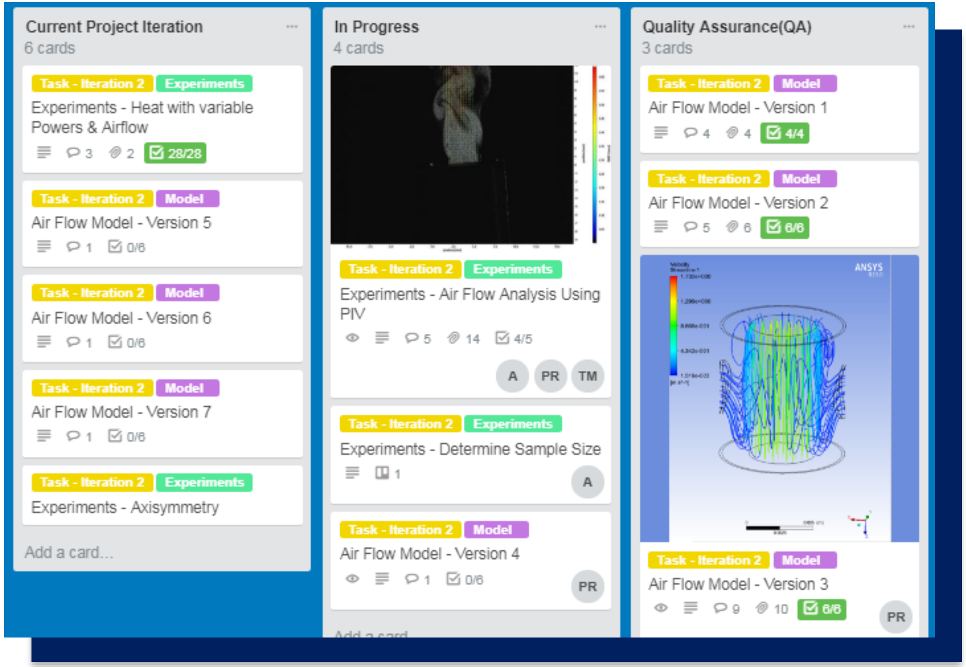
- **Time:** 3 months
- **Theme:** Complete Entire Project
- **Completed Items:**
  - Goal:
    - CFD model of an e-cigarette device
    - End to end integration of VVUQ
  - Model Design:
    - Commercial Software = ANSYS – CFX
    - Physical System Simplifications
    - Focus on heat profile within the system
  - Created PIRT Version 1
  - Exploratory experiments for system understanding
- **Entire project was <u>NOT</u> completed**



Note: In "Speculate" of **Iteration 2** the theme for **Iteration 1** was updated from ***Complete Entire Project*** to ***Exploratory***

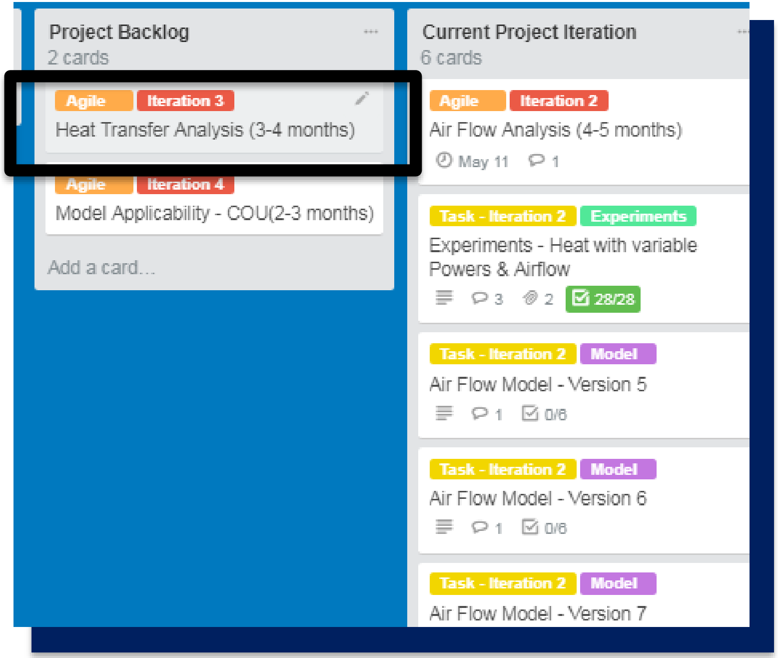
Iteration – 2(*Current*)

- **Time:** 4-5 months
- **Theme:** Airflow Analysis
- **Re-plan:** *(IF NECESSARY)*
  - Project Break Down: 4 Iterations
  - PIRT Update: Versions 4-6
  - Goal Specification: Question of Interest, Context of Use, Risk Assessment
  - Establish Credibility Goal(CG) Gradation
  - Experimental Design based on CG
  - Model Design: Airflow model Version 1-7 (Based on System Complexity)
- **Anticipated Completed Items**
  - CFD Airflow Model
  - Airflow Comparator Experiments
  - Model Assessment (Airflow ONLY)
  - Validated Review (Validation domain for airflow ONLY)



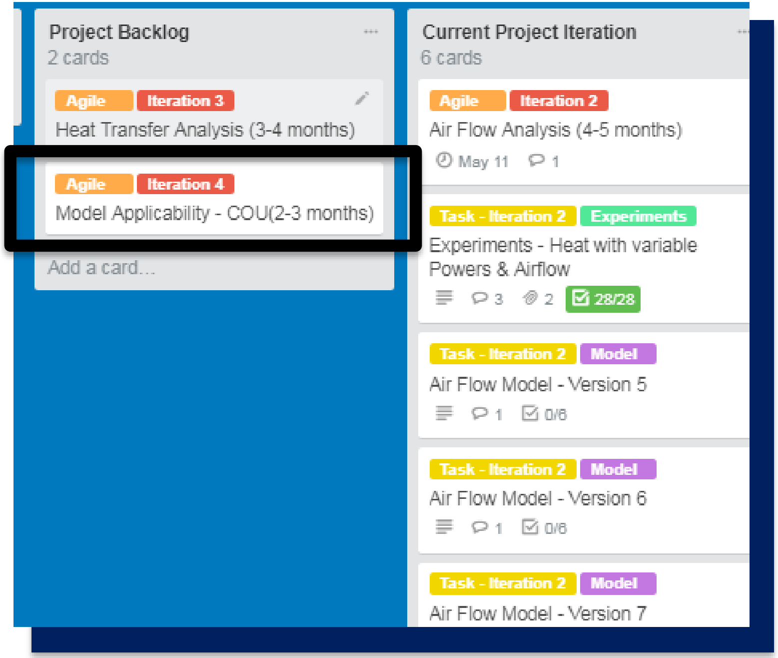
Iteration - 3

- **Time:** 3-4 months
- **Theme:** Heat Transfer Analysis
- **Re-plan:** (***IF NECESSARY***)
- **Anticipated Completed Items:**
  - Working CFD Heat Transfer Model
  - Comparator Experiments specified in Credibility Goals
  - Model Assessment
  - Validated Review (Validation domain for Heat Transfer)



Iteration - 4

- Time: 2-3 months
- Theme: Applicability Assessment
- Re-plan: (***IF NECESSARY***)
- Anticipated Completed Items:
  - CFD Heat Transfer with Air Flow Model – Modified for COU
  - Justification for extrapolating from Validation Domain to COU Domain
  - Review (COU domain for Model)



PIRT – Version 1

Phenomena	Importance	Confidence/Knowledge
Electral Power Input into heat		
Porosity		
Device Geometry		

PIRT – Version 2

- Added Notes Column
- Redefined Phenomena Column

Phenomena	Importance	Confidence/Knowledge	Notes
Airflow through cylinder			Entire system
Temperature through out system			Measured using thermocouples
Laminar flow			Based on Reynolds number calculation
Wick Difussion			None(will change)

PIRT – Version 3

- Split Confidence/Knowledge Column into 2 Columns

Phenomena	Importance	Confidence	Knowledge we have about what we're simulating	Notes
Airflow rate through cylinder	1			Entire system
Nature of the air flow through the atomizer (tube) (assume it's laminar)	1	but the confidence is low; may need to do some experiments to confirm	we have some knowledge about the nature of the flow // maybe the entrance of the flow matters more?	Based on Reynolds number calculation
Properties of Air	1		know the viscosity as a function of temp.	constant properties or time varying
Temperature through out system	1			Measured using thermocouples

PIRT – Version 4

- Added Our Ability to Simulate Column

Phenomena	Importance	Confidence	Knowledge we have about what we're simulating	Our ability/knowledge to actually simulate it	Notes: Ahmad & Paulina	Notes
Airflow rate through cylinder (puff profile)	1	High	Measured airflow rate put into the system.	airflow inlet boundary condition	elocity	Entire system
Nature of the air flow through the atomizer (tube) (assume laminar)	1	Low	mouthpiece particle velocity with PIV Note: May need experiments to confirm Laminar Flow	CFD model of airflow only (NO Heat) to better characterize & understand airflow	**Single phase**: polystyrene eads **Dual phase:** smoke articles (if detectable in PIV)	Based on Reynolds number calculation
Properties of Air	1	High	know the viscosity as a function of temp,	Ideal Gas Properties/Laws	deal Gas for air introduced nto the system. Outlet mouthpiece is air with mall particles/smoke	constant properties or time varying
Temperature through out system	1(Output)	Medium	Air/smoke temperature profile	Physical Laws	t different locations inside	Measured using thermocouples

PIRT – Version 5

- Added Type of Phenomena Column
- Split Confidence Column into 2 Columns

Type of Phenomena	Phenomena	Importance	Confidence in Importance	Confidence in Knowledge	Knowledge we have about what we're simulating	Our ability/knowledge to actually simulate it	Notes
Driving Physics??	Conservation of mass/momentum/energy	1	High	High	Laws are solid. No negotiation.	Laws already integrated in software.	ANSYS
Condition	Mode of operation: constant power or constant temperature	1	Medium	High	high knowledge	Upload the measured power profile as the heat source. Note: Can be used for both modes even though the power profile is different.	constant power assumes constant heat source; constant temperature requires feedback Temperature Mode: (a) off: expect to have constant power output. (b) on: power varies to keep Temperature constant
Output	Temperature through out system	1	High	Medium	Air/smoke temperature profile	Physics Laws	Measured using thermocouples. At different locations inside the atomizer and mouthpiece.
		1	High	Medium	Heating Coil Temperature/Heat Source	Physics Laws	Measured using thermocouples Attach thermocouples to the coil using cement
Output & Input ??	Nature of the air flow through the atomizer (tube) (assume it's laminar)	1	Medium	Low	mouthpiece particle velocity with PIV Note: May need to do some experiments to confirm Laminar Flow	CFD model of airflow only (NO Heat) to better characterize/understand airflow	Based on Reynolds number calculation. **Single phase**: polystyrene beads **Dual phase**: smoke particles (if detectable in PIV)

PIRT – Version 6

- Added *How to Improve Confidence in Knowledge* Column
- Reordered items 1-14

Type of Phenomena	Phenomena	Importance	Confidence in Importance	Confidence in Knowledge	Knowledge we have about what we're simulating	Our ability/knowledge to actually simulate it	How to Improve Confidence in Knowledge	Notes
Input	Conservation of mass/momentum/energy	1	High	High	Laws are solid. No negotiation.	Laws already integrated in software.	N/A	ANSYS
Input	Mode of operation: constant power or constant temperature	1	Medium	High	high knowledge	Upload the measured power profile as the heat source. Note: Can be used for both modes even though the power profile is different.	N/A	constant power assumes constant heat source; constant temperature requires feedback Temperature Mode: (a) off: expect to have constant power output. (b) on: power varies to keep Temperature constant
Output	Temperature through out system	1	High	High	Air/smoke temperature profile	Physics Laws	Experiment for verification validation	Measured using thermocouples. At different locations inside the atomizer and mouthpiece.
		1	High	High	Heating Coil Temperature/Heat Source	Physics Laws	Experiment for verification validation	Measured using thermocouples Attach thermocouples to the coil using cement
Output	Nature of the air flow through the atomizer (tube) (assume it's laminar)	1	Medium	Low	mouthpiece particle velocity with PIV Note: May need to do some experiments to confirm Laminar Flow	CFD model of airflow only (NO Heat) to better characterize/understand airflow	Experiments using PIV	Based on Reynolds number calculation. **Single phase**: polystyrene beads **Dual phase:** smoke particles (if detectable in PIV)
Input	Airflow rate through cylinder (puff profile)	1	High	High	Measured airflow rate put into the system.	airflow inlet boundary condition	N/A	Entire system, Velocity