V&V 40 Subcommittee

V&V for Computational Modeling for Medical Devices

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SETTING THE STANDARD

The Role of CM&S for Medical Devices

CM&S embedded in a medical device e.g., physiological model in a control system

CM&S as valid scientific evidence

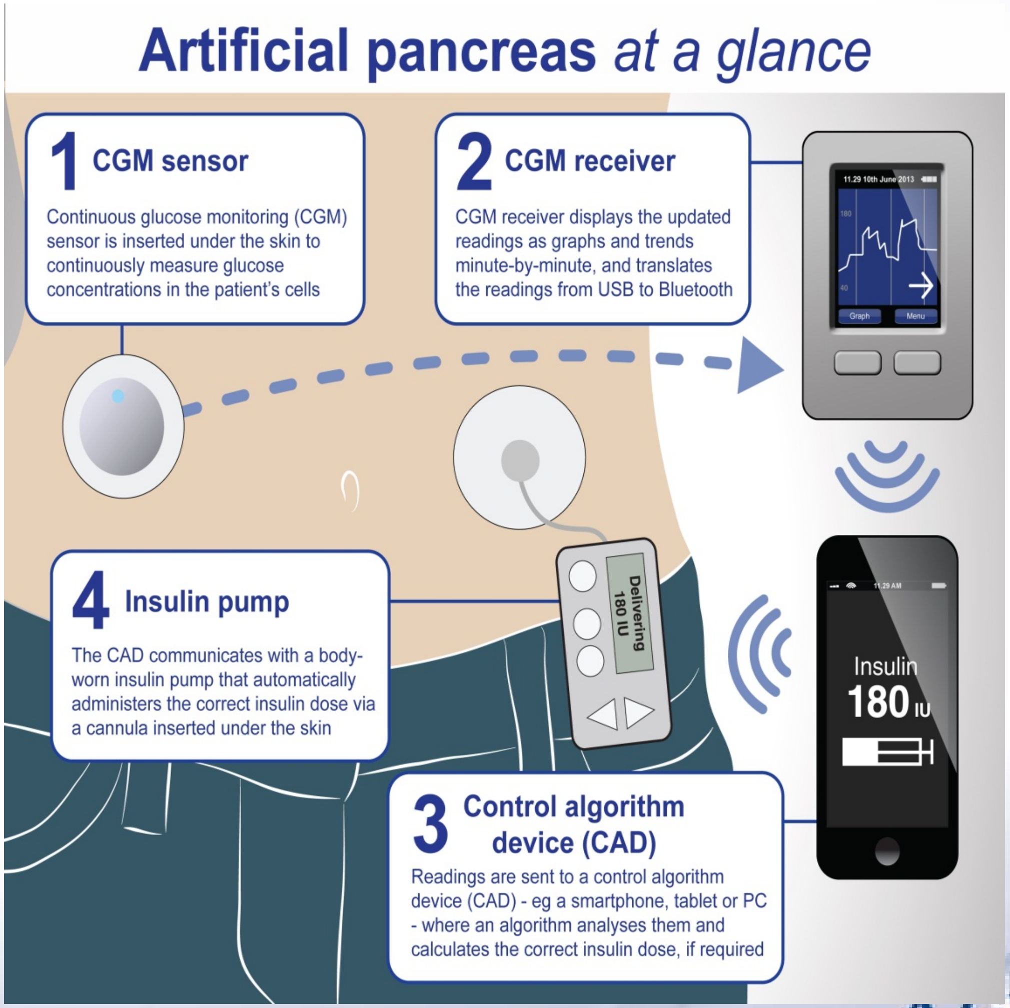
e.g., fatigue safety factors

CM&S is the medical device

e.g., clinical decision support

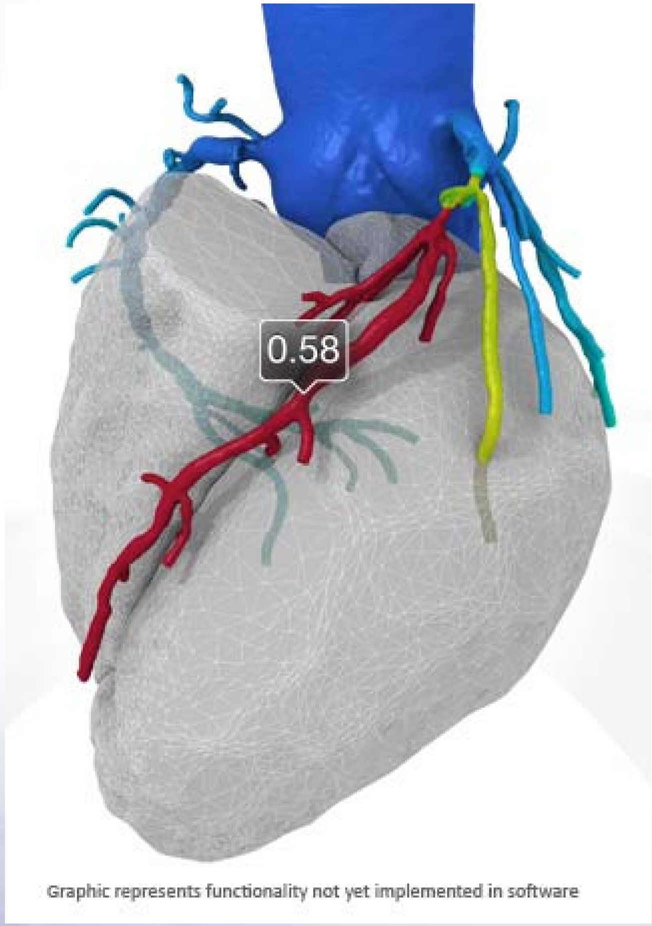
The Role of CM&S for Medical Devices

CM&S embedded in a medical device e.g., logical algorithm in a control system



medicalnewstoday.com

The Role of CM&S for Medical Devices



heartflow.com

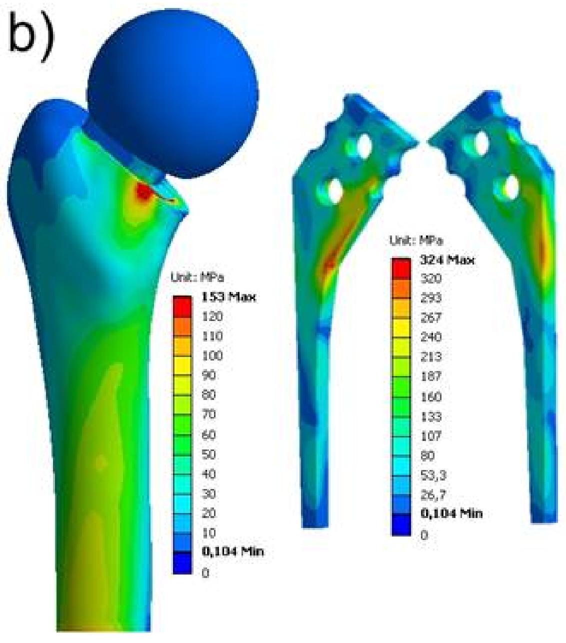
CM&S is the medical device

e.g., clinical decision support

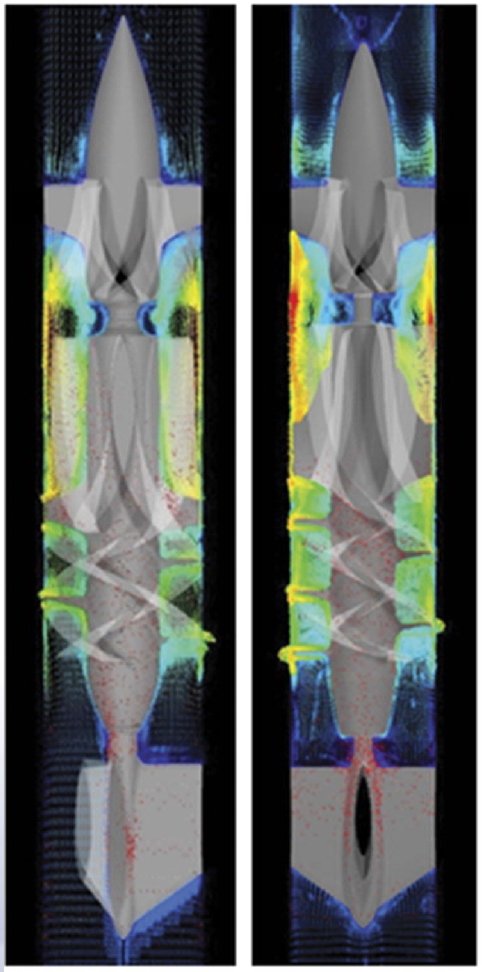
The Role of CM&S for Medical Devices

CM&S as valid scientific evidence

e.g., fatigue safety factors



Kelm, Int J of Med Sci 2009



Bluestein, PLOS - 2012

Credible CM&S

In order to more fully leverage CM&S of medical devices (medical products), we need a methodology to ensure the output of CM&S is credible.

Credibility: the quality to elicit belief or trust in predictions of the CM&S within a context of use

Adequate verification, validation and uncertainty quantification (VVUQ) are necessary to foster confidence and wider acceptance of CM&S in medical device evaluation.

Stakeholders need a tool for determining and communicating the rigor of VVUQ needed to support the use of CM&S in

- Product development
- Regulatory submissions
- Medical Device Development Tools[1] qualification applications
- FDA Library of Models and Simulations[2]

1, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm374427.htm
2, http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346375.htm

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ASME Guide for V&V for CM&S

Focus of the Guide

Instead of focusing on HOW TO perform V&V (established elsewhere)

The main emphasis of the *credibility strategy* is to serve as a framework for determining the risk associated with using a computational model in a specific context of use to inform decision making and for determining 'HOW MUCH' V&V is necessary to support the model in that context of use[3].

3, https://standards.nasa.gov/documents/detail/3315599

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The Credibility Strategy

Establishing credibility involves

- assessing the pedigree of input data
- verifying the software
- verifying calculations
- determining an appropriate comparator
- validating the CM&S outcomes with an appropriate comparator
- quantifying uncertainty
- performing sensitivity analysis to establish robustness
- determining the predictive capability of the CM&S for the context of use (COU)

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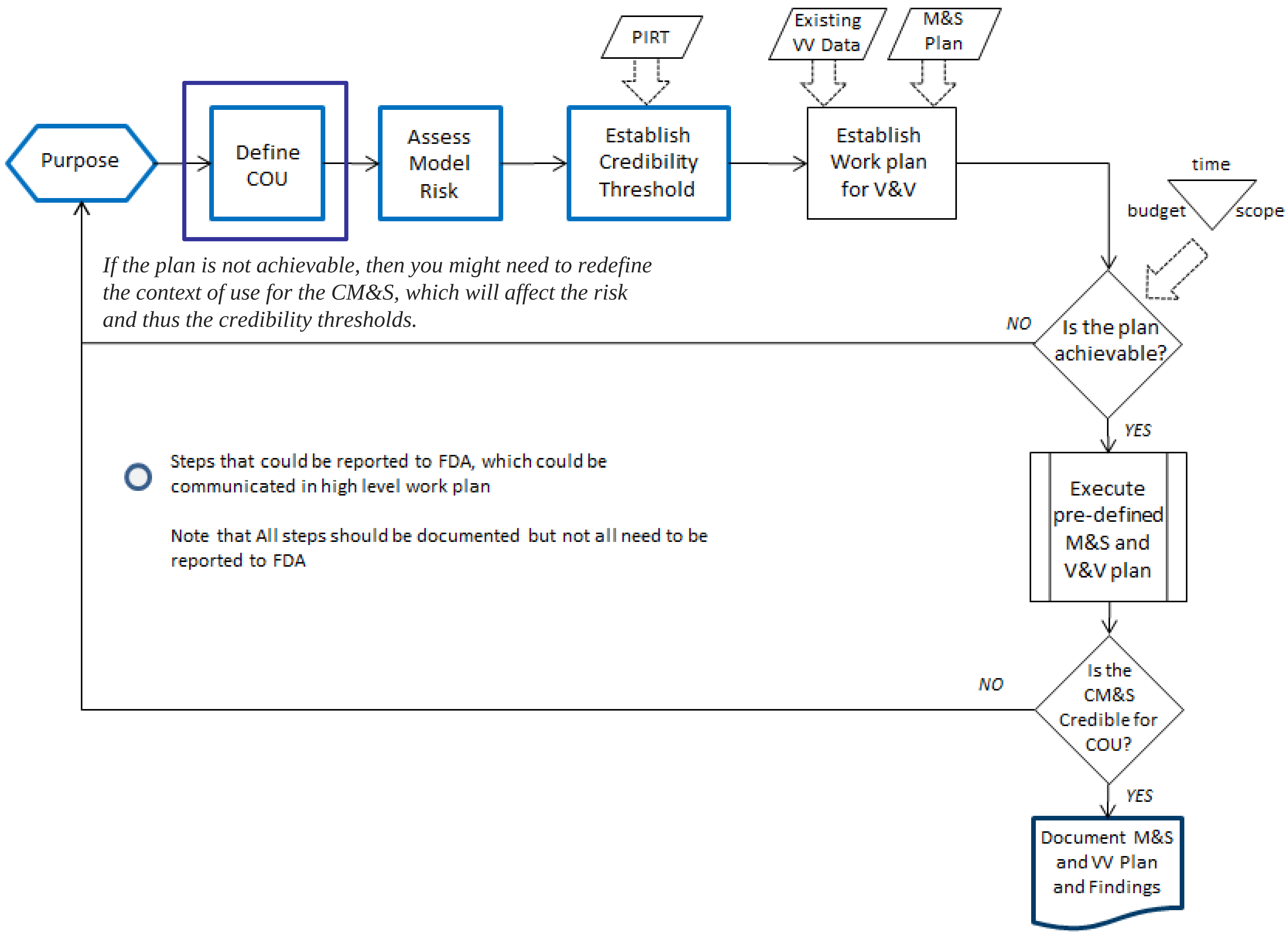
Credibility Strategy Overview

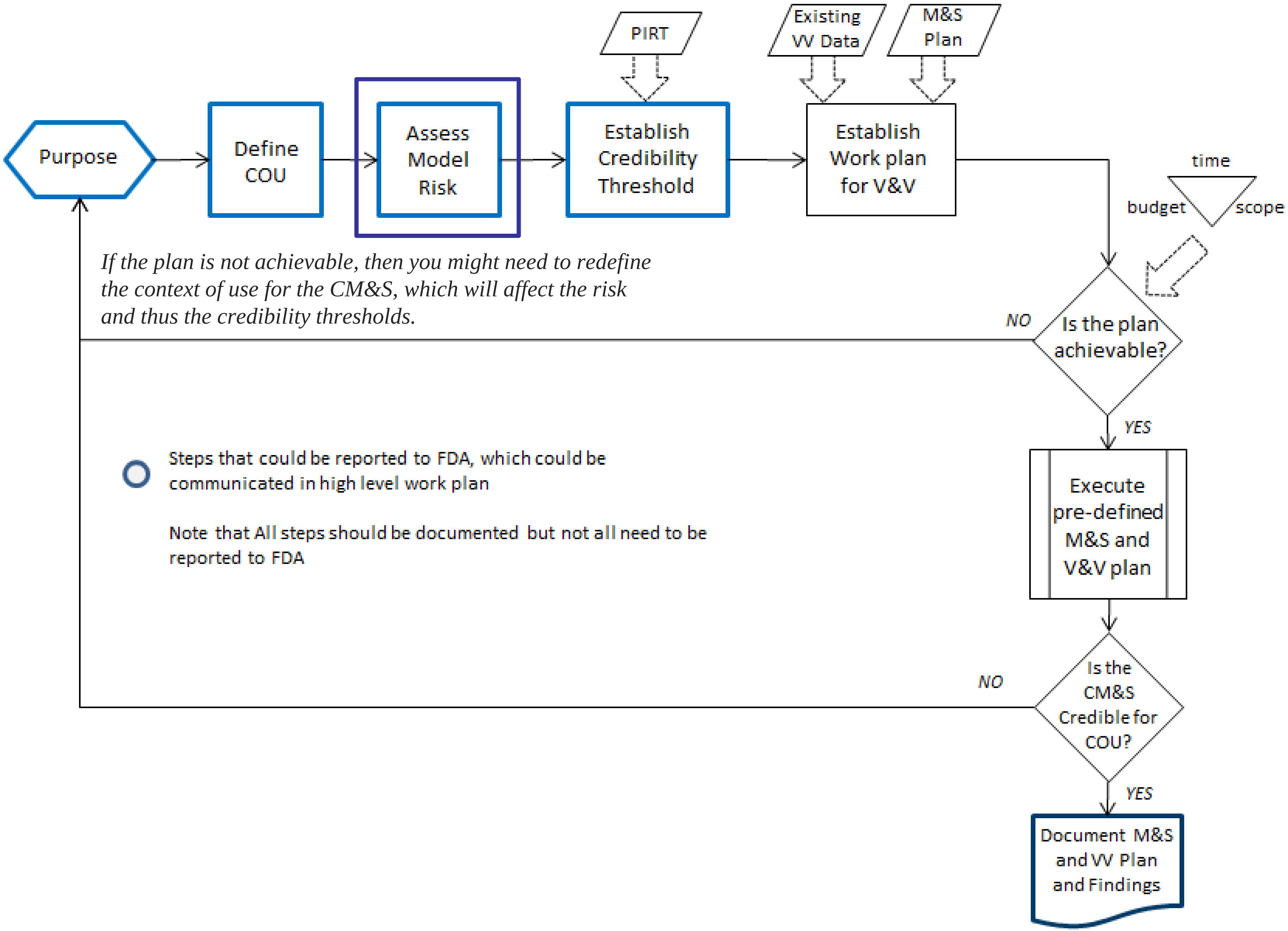


Computational Fluid Dynamics

Example COU

For a marketing application, computational fluid flow simulation is used to characterize the flow field and predict blood damage and thrombosis potential for a circulatory support device (e.g., heart valve, blood pump).

Credibility Strategy Overview

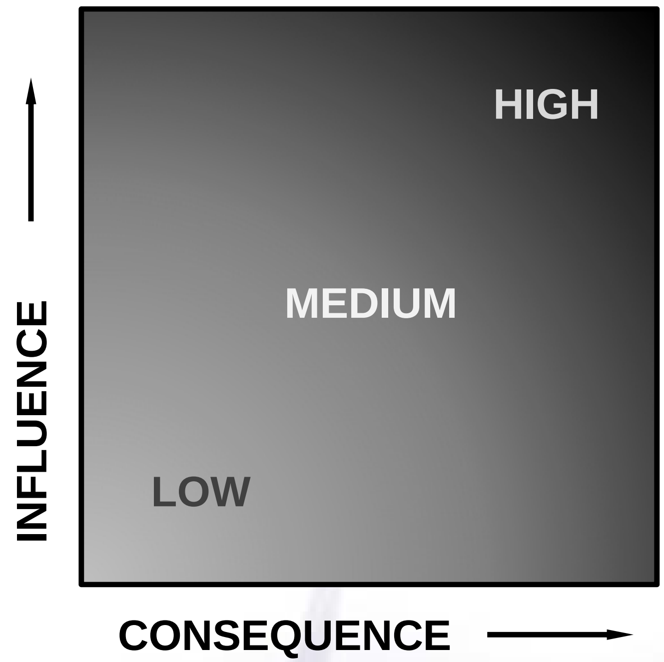


Risk Assessment

Establish Context of Use

CM&S Risk: combination of decision influence and consequence

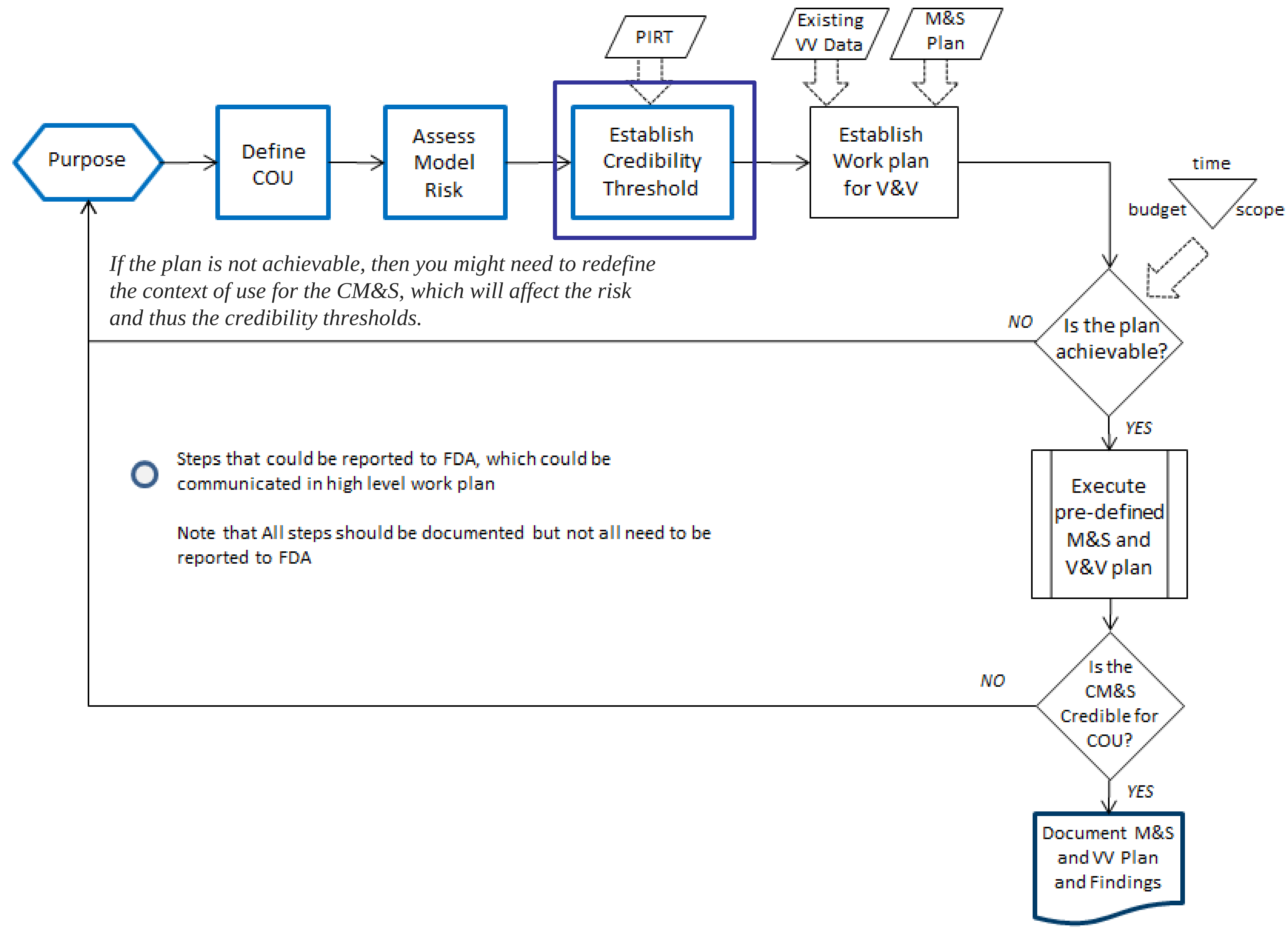
- **Decision Influence:** contribution of CM&S outcome to the decision being made
- **Consequence:** impact if the CM&S outcomes prove incorrect



Risk assessment

- Directs/guides V&V activities
- Defines model credibility thresholds

Credibility Strategy Overview



Framework to Assess Credibility

Ensure that the credibility of the CM&S is commensurate with the associated risk

The questions raised by the FAC are the following:

- How are the elements of the CM&S represented?
- How well is the comparator understood (e.g., experiment)?
- How appropriate is the computational model to the comparator?
- How rigorously are the outputs compared?
- How do the CM&S and VVUQ activities relate to the context of use?

Evolution – take 1

April 2012

"Level"	Verification	Computational Model					Comparator		Validation
		Device Geometry	Constitutive models/Governing Equations Used	Boundary Conditions, Loads and Deformations	Uncertainty assessment	Sensitivity assessment	Physiological Geometry	"Experimental" Design	some accuracy assessment btwn the CM & comparator
1									
2									
3									
4									
5									

Complete V&V Assessment / Evaluation Criteria

(red)	Unsophisticated, but applicable for "low risk" applications, early in design phase/submission process etc.
(yellow)	Moderately sophisticated - applicable for "moderate risk" application etc.
(green)	Sophisticated - applicable for "high risk" application etc.

Evolution – take 2

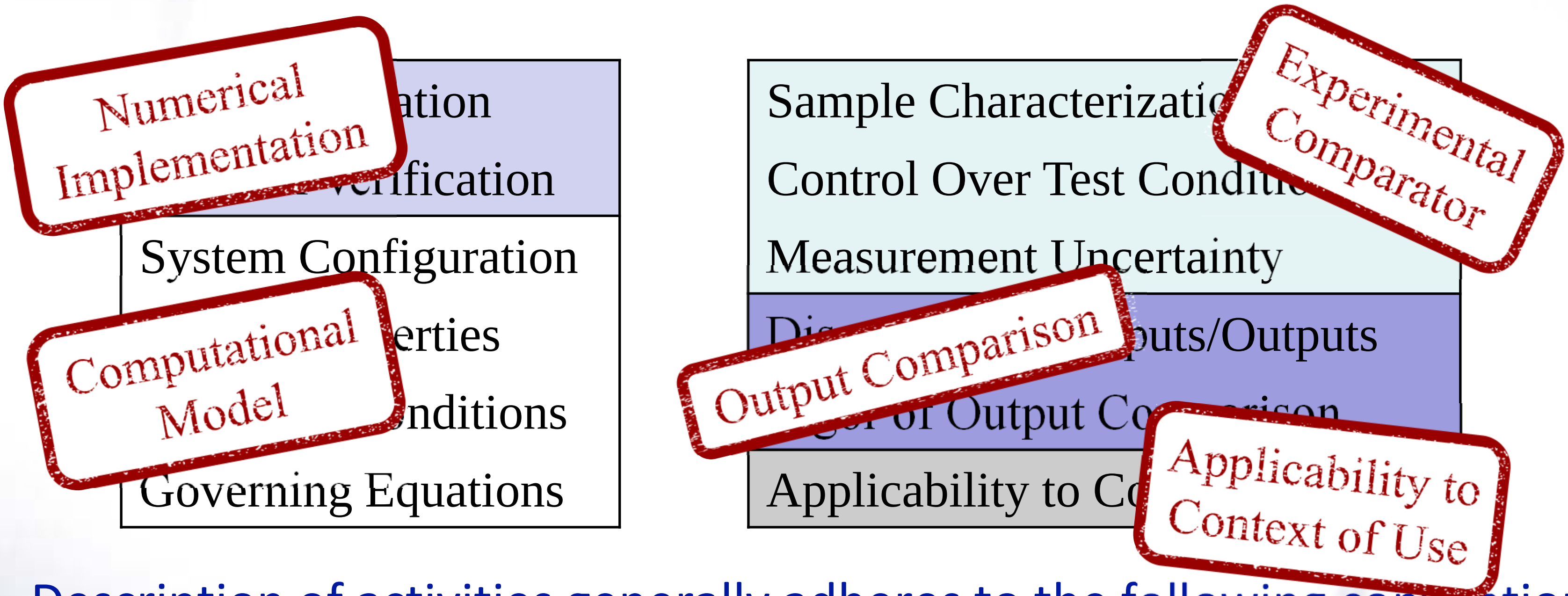
September 2012 & February 2013

LEVEL	VERIFICATION*		VALIDATION								ASSESSMENT		
			Computational Model				Evidence-based Comparator				Discrepancy	Comparison	Applicability
	Code	Solution	System Configurat	Governing Equations	System Properties	System Conditions	System Configuration	System Properties	System Conditions	Sample Size	Model-to-Comparator	Qualitative or Quantitative	V&V to COU
0	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete	Insufficient Incomplete
1	Judgment based on prior similar analysis	Judgment based on prior similar analysis	Little or no representation	Physics substantially simplified relative to theory, with expected order of magnitude effect	Bulk properties	Significant simplification of BCs with substantial effect on QOI	Locations for data collection are roughly measured or estimated	Material properties are nominal average and homogeneous non-specific to parent system	System states are not specifically prescribed, measured and affected degrees of freedom are unknown		Model and comparator data might not correspond to equivalent conditions		Abstraction of CoU that approximates essential system properties
	Minimal test of any software elements	Numerical errors have an unknown or large effect on simulation results	Abstraction of geometry/ architecture	Model forms are either unknown or fully empirical	Simplified properties over known comparator	Key BCs not modeled	Geometry of parts and assemblies is assumed	Material interactions are non-specific to the system when used to derive reported quantities	OR	Single case OR few cases with no variation of key parameters	AND	Qualitative comparison only with comparison is of discrete rather than continuous variables	
	Little or no SQE procedures specified or followed			No coupling	Uncertainties and sensitivities are not addressed	Uncertainties and sensitivities are not addressed	Calibrated system where error of system is estimated OR Signal to noise ratio is on the order of data	Environmental conditions unknown and effects on materials not accounted for	Perturbations are approximate		Report different but related QOI		
2	Code is managed by SQE procedures	Numerical effects on relevant SRQs are qualitatively estimated	Mean/ nominal geometry	Physics substantially simplified with minor effect on QOI	Bulk properties, not confirmed or approximation of comparator	Some simplification of BCs with a considerable effect on QOI	Locations for data collection are prescribed and measured	Material properties are nominal average and homogeneous specific to the system tested	System states are specifically prescribed and measured and affected degrees of freedom are known	Several cases with varied key parameters	Model and comparator data do not correspond to equivalent conditions	Qualitative comparison only with comparison of trends possible from continuous variables	Approximates key CoU features and captures essential system properties
	Unit and regression testing conducted	Input/ Output verified by the analysis	Single case	Model forms are based and calibrated/ tuned on data from related systems	Nominal properties	Binary variation	Geometry of parts and assemblies is coarsely measured	Material interactions are specific to the system when used to derive reported quantities	OR	OR	AND		
	Some comparisons made with benchmarks		Abstract geometry range of deterministic cases	Little or no coupling	Distribution of simplified properties	Uncertainties propagated with informal sensitivity analysis	Calibrated system where error of system is known OR Signal to noise ratio is substantially greater than one.	Environmental conditions known but effects on materials not accounted for	Perturbations are prescribed and measured	Statistically relevant sample size for constant key parameter(s)	Report the same QOI	OR	
			Major features captured		Uncertainties propagated with informal sensitivity analysis							Quantitative comparison of single, achievable case	
3	Some algorithms are tested to determine the observed order of numerical convergence	Numerical effects are quantitatively estimated to be small on some SRQs	MMC and LLC	Minor simplifications of physics with at most minor effect on QOI	Distribution of properties, confirmed as representative of comparator	Representative BCs with minor effect on QOI	Locations for data collection are prescribed and error in location is collected	Key material properties are measured for this lot/ billet and heterogeneity captured where appropriate	System states are specifically prescribed and measured and affected degrees of freedom are known	Several cases with varied key parameters	Model and comparator data correspond to equivalent conditions	Quantitative comparison of continuous key QOI, without predictive accuracy or uncertainties available OR	Embodies key CoU features and captures key and associated system properties
	Some features & capabilities are tests with benchmark solutions	Input/ Output independently verified	Multiple cases, range not statistically determined	Model representation of all important processes	Uncertainties segregated, propagated and identified in QOI	Variation not statistically relevant	Geometry of parts and assemblies is measured to machine tolerance	Material interactions are measured when used to derive reported quantities	AND	AND	AND		
	Some peer review conducted	Some peer review conducted	Major and some minor features captured	Calibration/ tuning needed		Uncertainties segregated, propagated and identified in QOI	Error of system is calculated based on manuf. calibration, and signal to noise ratio is high	Environmental effects on key materials accounted for	Perturbations are prescribed and measured	Statistically relevant sample size for key parameter(s)	Report same QOI	Quantitative comparison with broad range of cases	
			Deterministic cases	Some couple, when relevant									
4	All important algorithms are tested to determine the observed order of numerical convergence	Numerical effects are determined to be small on all important QOIs at conditions/ geometries directly relevant to the context of use	No simplification	Key physics captured	Key properties captured with statistical distributions, confidence intervals	No simplifications	All dimensions/ assemblage known to greater than machine precision	All material properties are measured for lot/ billet and heterogeneity captured where appropriate	System states are specifically prescribed and measured and affected degrees of freedom are known	Comprehensive parameter variability	Model was implemented with the equivalent comparator conditions	Quantitative assessment with predictive accuracy, experimental	
			Multiple cases, ranges statistically relevant to samples	Reduced model form error		Appropriate distribution of variation	Data is collected from locations known with high precision	Material interactions are measured with tolerance when reporting derived quantities	AND	AND	AND	AND	Embodies all properties in context of use
	All important F&Cs are tested with rigorous benchmark solutions	Experimental uncertainties are well characterized	All features captured	Minimal need for calibration/ tuning	Match properties with relevant uncertainty and comprehensive	Comprehensive sensitivity analysis conducted for BCs	Error of system is measured a priori and signal to noise ratio is high	Environmental effects on all materials accounted for	Perturbations are prescribed and measured	Statistically relevant sample size for all parameters	Report same QOI AND	Computational uncertainties are well characterized	
			Full geometry						AND				

Evolution – take 3

Feb 2014

Framework to Assess Credibility



Description of activities generally adheres to the following convention, in order to provide relative assessments of activities that can improve credibility:

- <low credibility>
- …
- <improved credibility>
- …
- <high credibility>

Credibility Factor Thresholds

Example

Quantification of sensitivities: Associated activities reflect the degree to which CM&S results are sensitive to inputs including material properties, geometries, and boundary conditions.

- Sensitivity analyses were not performed
- Sensitivity analyses on expected key input parameters were performed across the range of values expected in the COU
- Comprehensive sensitivity analysis was performed across the full range of all input values expected in the COU

Credibility Factor Thresholds

Example

Rigor of output comparison: Increased credibility is achieved by increased quantification and incorporation of uncertainties in the comparison of the outputs from the CM&S and comparator. Credibility relies on increased attention to *both* experimental uncertainty and computational error.

- Visual Comparison
- Comparison of simply measuring the differences between paired computational results and experimental data
- Comparison with uncertainty captured and incorporated from the comparator and/or computational model
- Comparison with uncertainties captured and incorporated from both the comparator and the computational model, including comparison error

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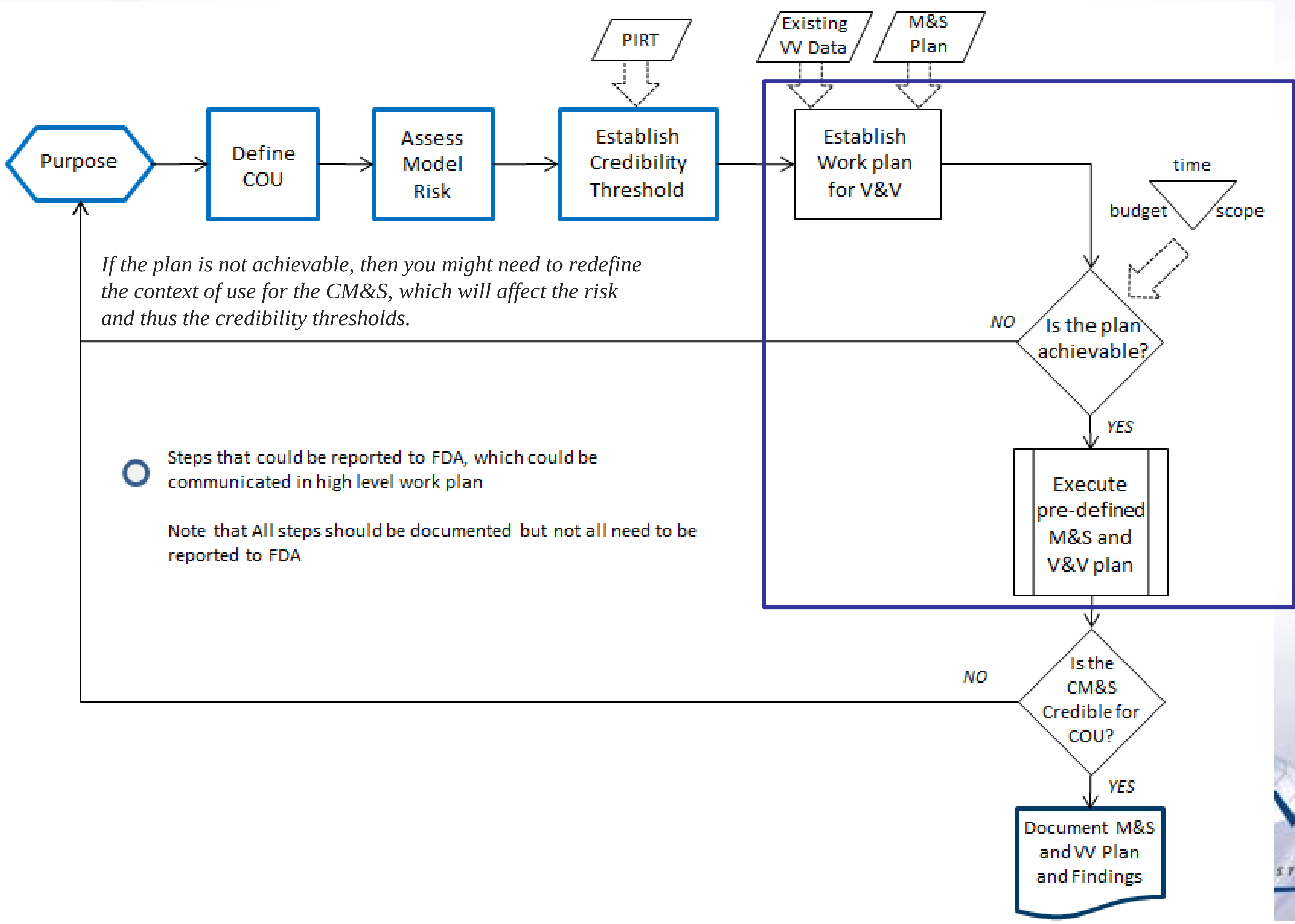
Credibility Strategy Overview



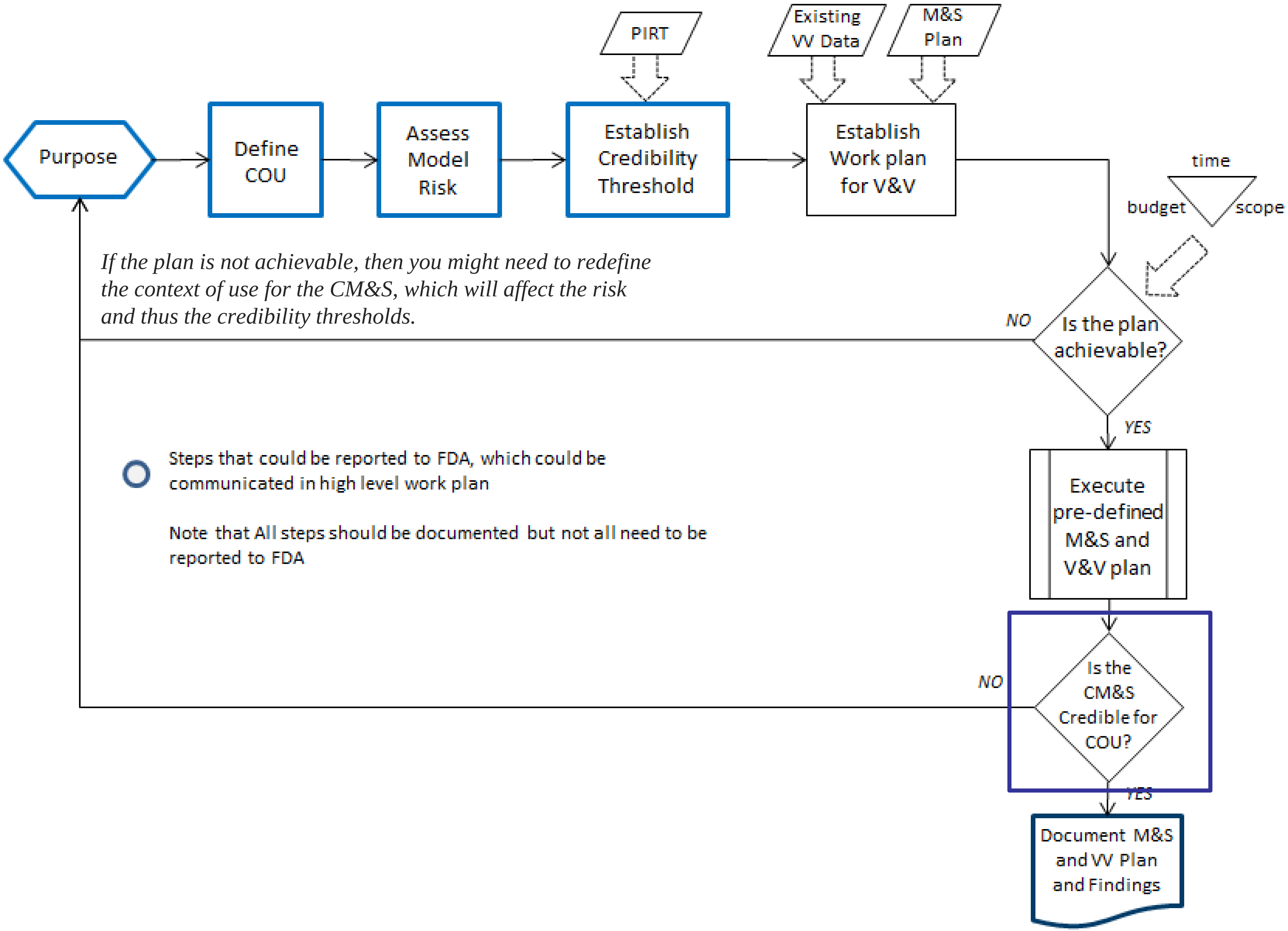
Establishing V&V Plan

Develop the V&V plan that considers:

- Explicit mention of the COUs
- Risk posture for the CM&S for the defined COUs
- Credibility thresholds, evaluation metrics, evaluation criteria and justifications
- V&V activities that will be implemented, and rationale for why the V&V activities are appropriate to satisfy the credibility thresholds
- Discuss the methods for acquiring and analyzing data that will be used, and rationale for why the data source, data quality and data analysis are appropriate or sufficient to satisfy the credibility thresholds

ASME V&V 10, ASME V&V 20

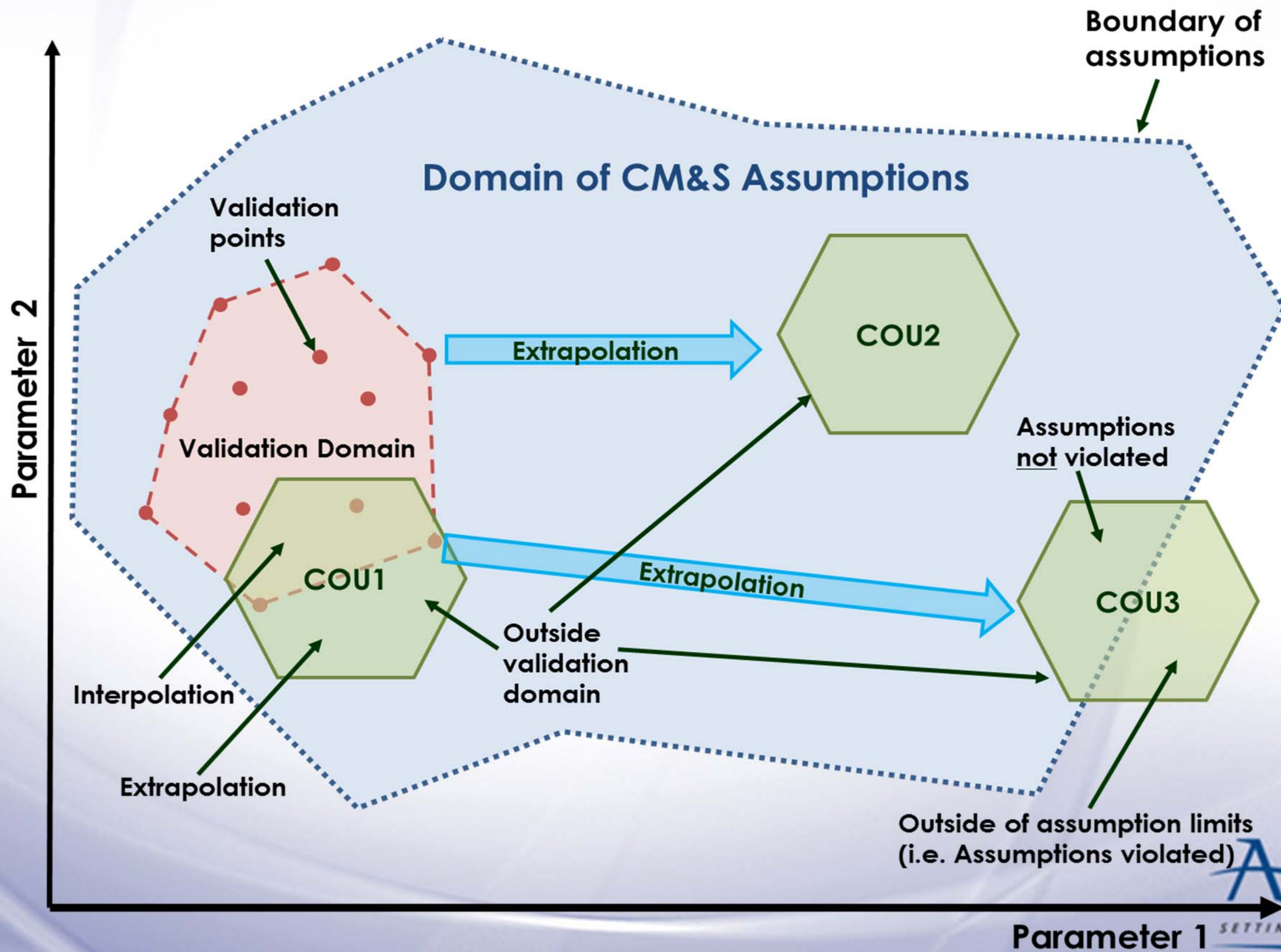
Credibility Strategy Overview



Steps that could be reported to FDA, which could be communicated in high level work plan

Note that All steps should be documented but not all need to be reported to FDA

Applicability of V&V Activities



V&V-40 Subcommittee Membership

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Andrew Pierce, Biomet
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Payman Saffari, NDC
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* Standards Committee representative

Subcommittee members in bold

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