Key Considerations for SaMD Companies Developing and Commercializing Software as Medical Devices

FEBRUARY 20, 2020

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Rook Quality Systems

Rook Quality Systems is a consulting firm dedicated to helping startup to mid-sized medical device companies develop and maintain effective and efficient quality systems.

We provide specialized and custom consulting services for all classes of medical devices, including medical software and combination devices.

Quality System Design

DHF/ TF Creation

Audit Support

Software Validation

Design Control

Risk Management

Regulatory Submission Support (Int'l)

Quality System Training

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Intro to Andrew Wu

ANDREW WU

BRANCH MANAGER / SOFTWARE CONSULTANT

Experienced R&D Engineer and Software Quality Assurance Engineer leading Class II Medical Devices to commercialization in the US

Served as Project Manager of multiple SaMDs intended to commercialize in the US and EU

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Agenda

- What is SaMD?
- Why is SaMD difficult to regulate?
- Recently cleared SaMD in the US
- Leverage Frameworks during SW development
- Regulatory Strategy informs SW development
- Recommendations to SaMD Manufacturers
- What is FDA looking for in premarket submission?

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What is SaMD?

SaMD Definition (IMDRF N10)

Software intended to be used for **one or more medical purposes** that perform these purposes **without being part of a hardware medical device**.

Intended Use of SaMD (IMDRF N12)

To identify the intended medical purpose of SaMD,

- Treat or diagnose
- Drive Clinical Management
- Inform Clinical Management

To state the healthcare situation or condition that the SaMD is intended for

- Critical
- Serious
- Non-Serious

To describe the core functionality of SaMD

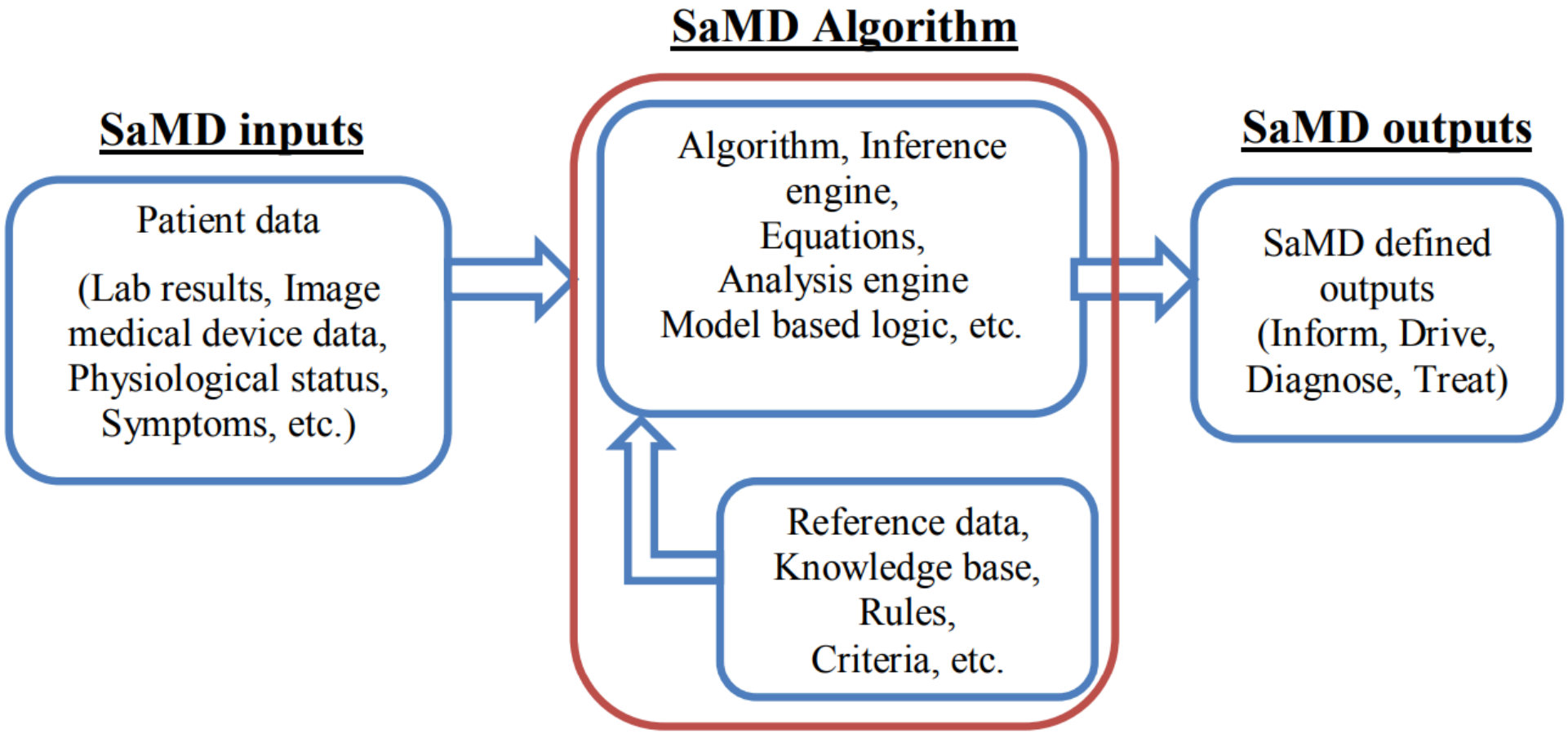

Figure 9 - SaMD Basic Programming Model

SaMD: Clinical Evaluation N41 (2017)

IMDRF Proposed SaMD Framework

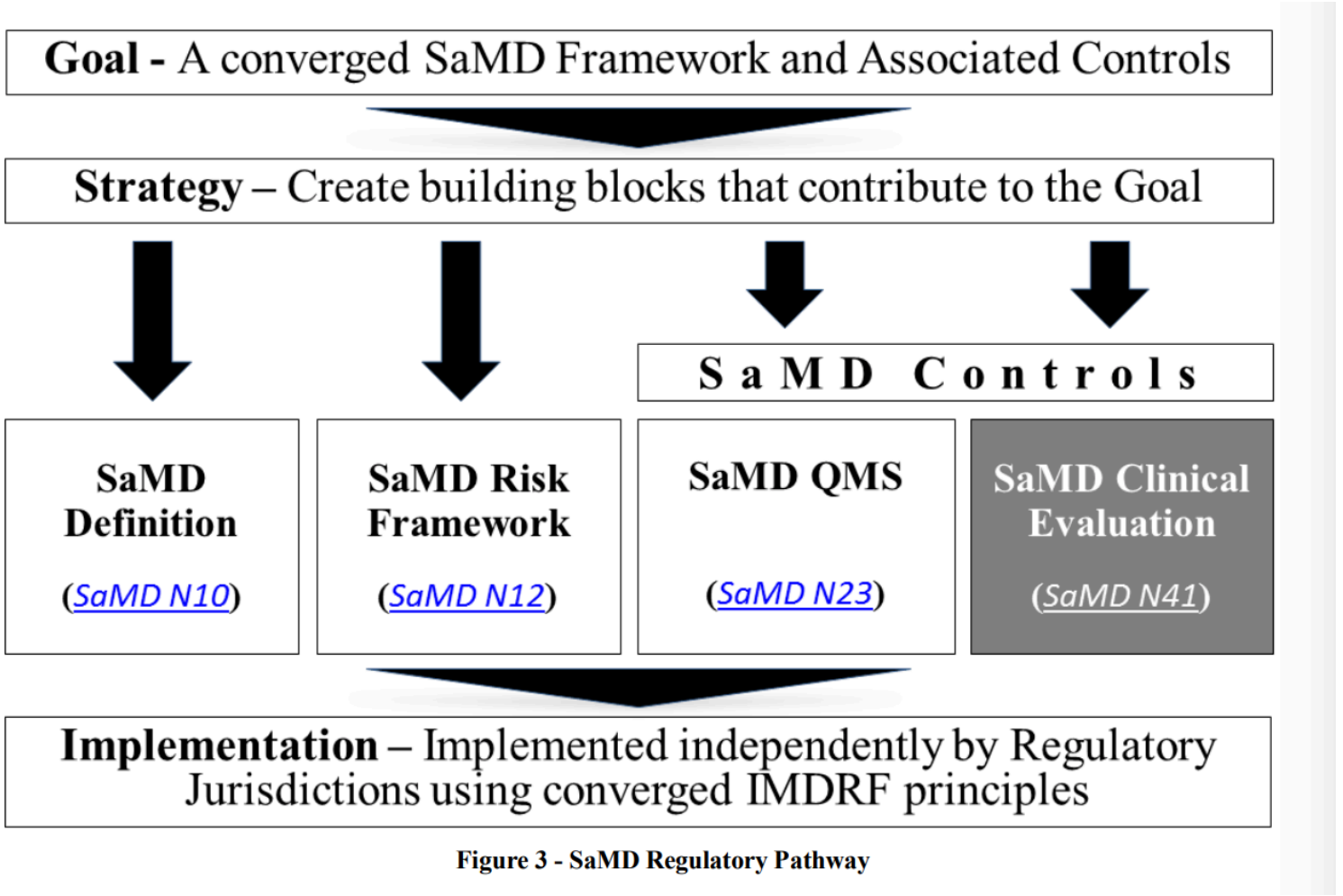

Figure 3 - SaMD Regulatory Pathway

SaMD: Clinical Evaluation N41 (2017)

FDA's take on regulating SaMD

- Enacted 21st century cures act in Dec 2016

- Issue digital health guidance and revise pre-existing guidance documents[1,2]

- Clinical Decision Support Software[2]
  - Provides HCPs and patients with information 'intelligently filtered or presented at appropriate times' to enhance healthcare
  - Whether HCP can independently review the basis of information or recommendations the software presents
  - FDA's draft CDS guidance states that rules-based AI could meet this standard by using publicly available clinical practice guidelines, published literature, FDA-approved labels, etc.

Reference:
(1) https://www.natlawreview.com/article/your-software-medical-device-fda-issues-six-digital-health-guidance-documents
(2) https://www.rookqs.com/post/2018/06/20/fda-s-take-on-digital-health-regulatory-paradigm-shift

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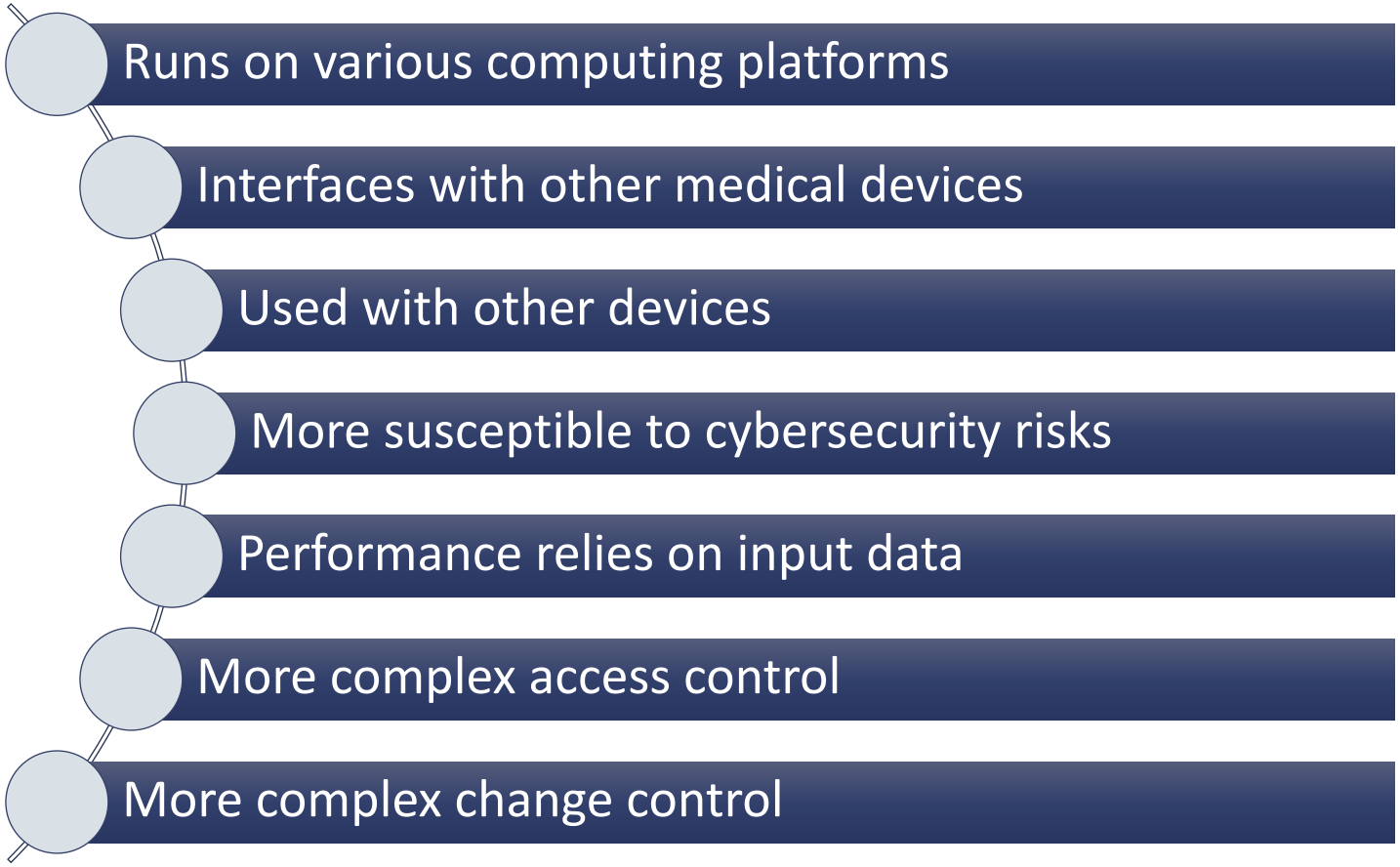
Why is SaMD difficult to regulate?

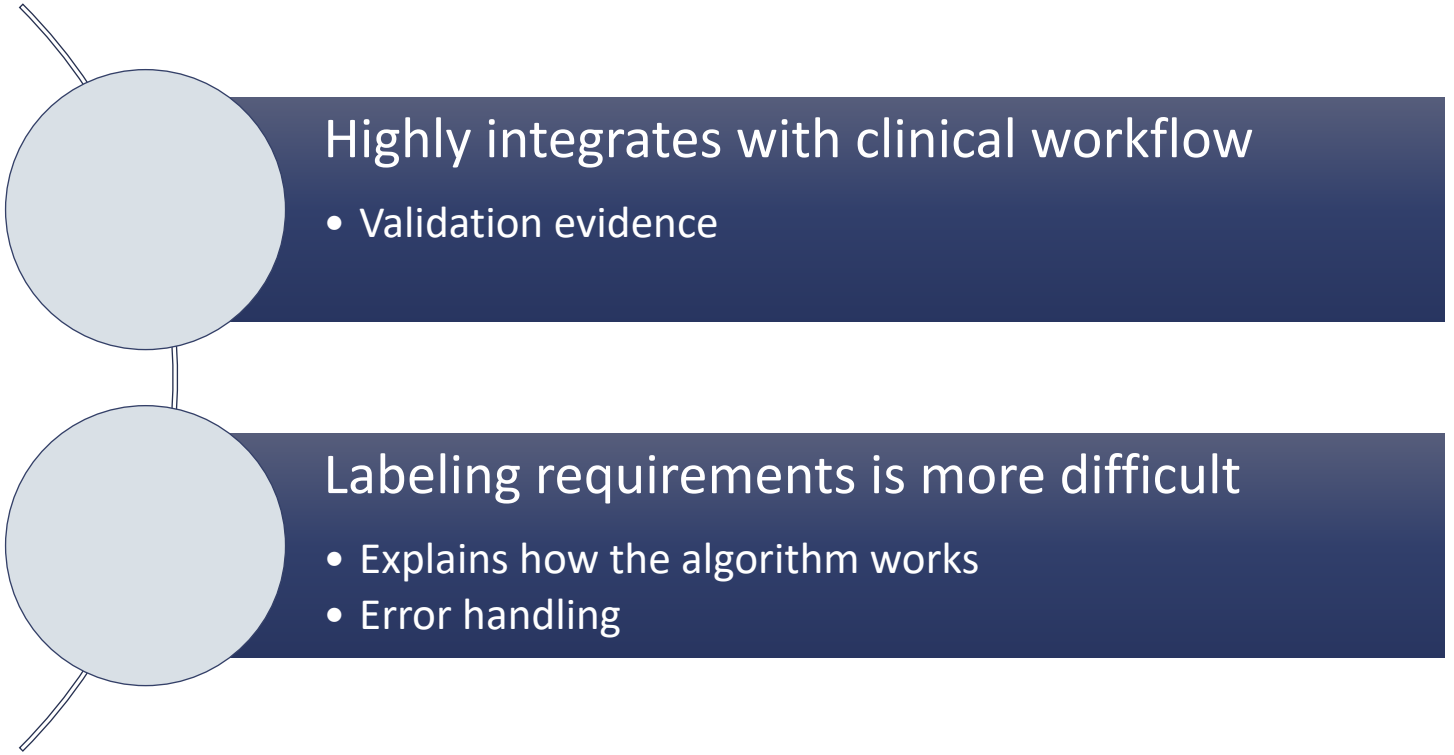
Why is SaMD difficult to regulate?

TECHNICAL CONSIDERATIONS



Why is SaMD difficult to regulate?

CLINICAL CONSIDERATIONS



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Recent FDA cleared SaMDs

Recent FDA cleared SaMDs overview

Viz.ai ContaCT (DEN170073)
A software for finding suspected large vessel occlusion from CT angiogram images

Heartflow Analysis (K190925)
A software for simulating coronary hemodynamics from CT angiogram

iDx-DR (DEN180001)
Automatically detect more mild diabetic retinopathy in adults diagnosed with diabetes

Caption Guidance
Acquisition of cardiac ultrasound images and uses artificial intelligence (AI) to provide real-time guidance.

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Leverage Frameworks

Leverage Frameworks

N23 SaMD QMS

- Traceability to 13485 sections

IEC 62304 Software lifecycle management

TIR 45 Agile Practice

Proposed GMLP framework

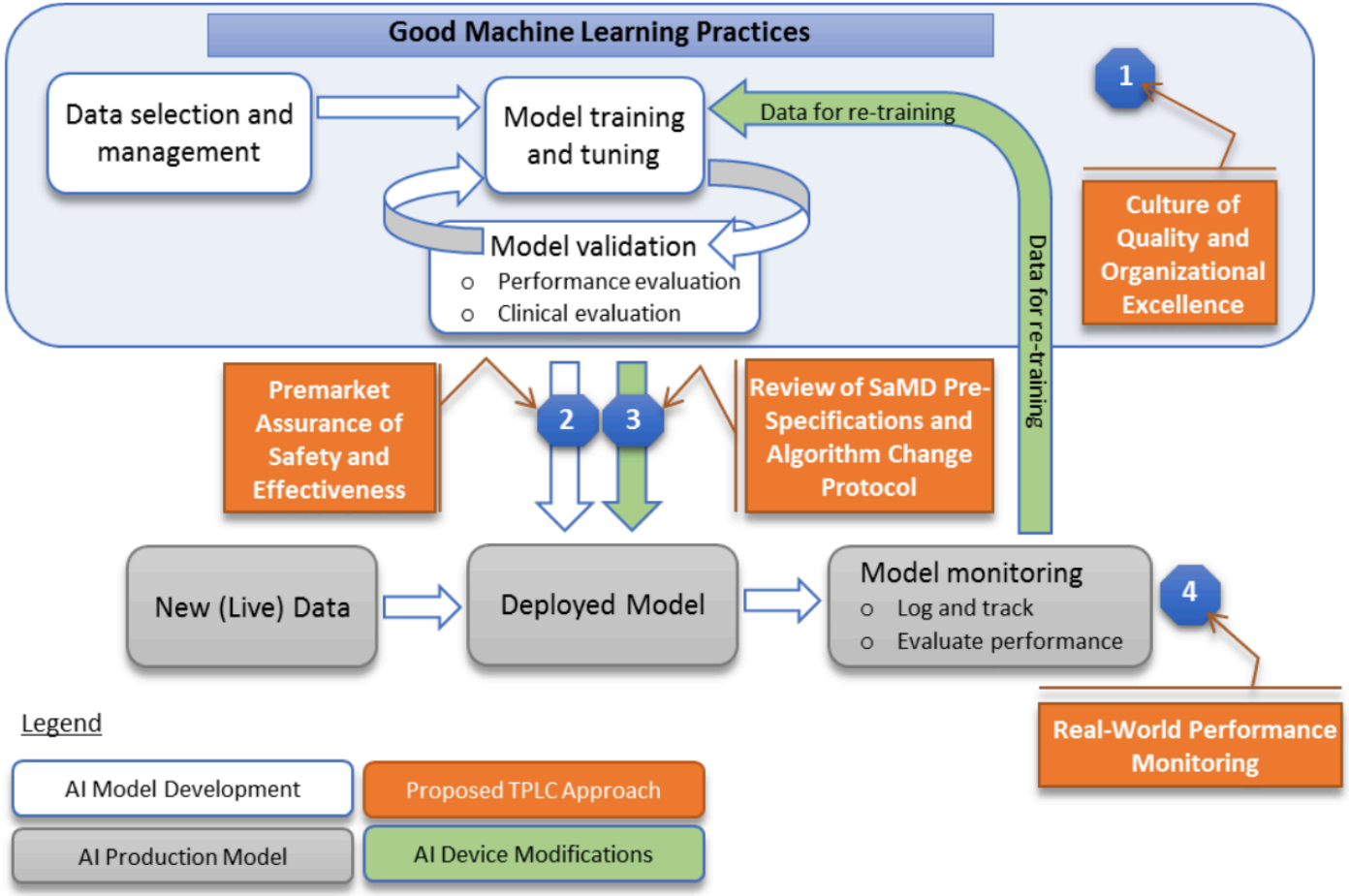

Figure 2: Overlay of FDA's TPLC approach on AI/ML workflow

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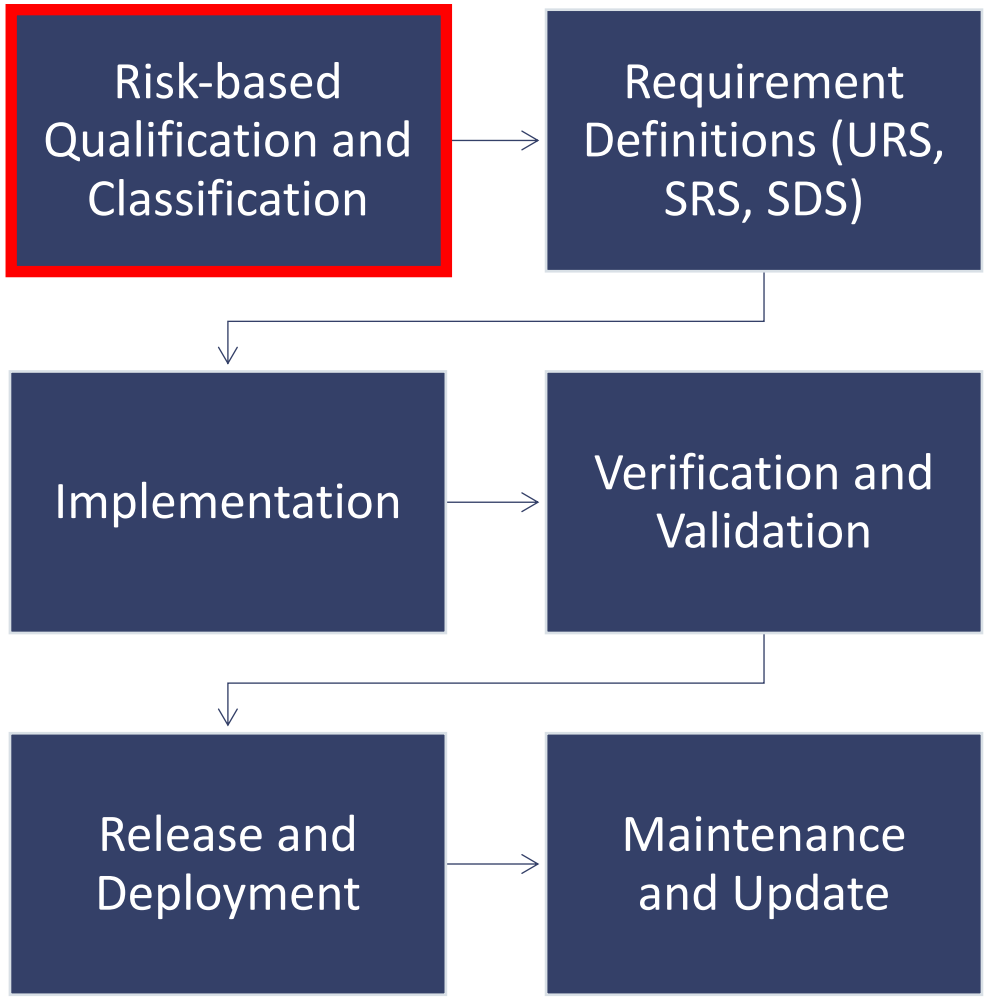
Regulatory Strategy informs SW Development

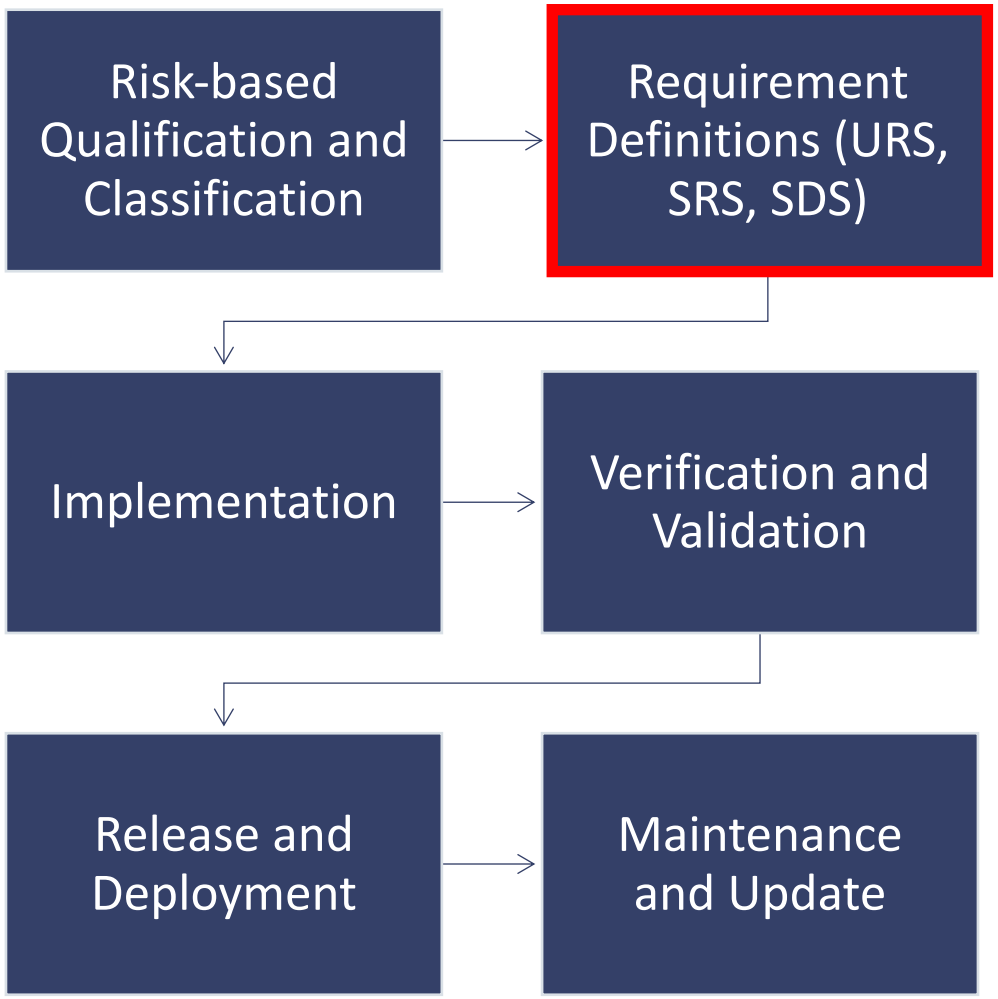
Regulatory Strategy inform software development strategy



Step 1 – Risk-based Qualification and Classification

- Cures Act
- CDS Guidance
- IMDRF N10 SaMD Definitions
- IMDRF N12 SaMD Risk Categorization
- Risk Analysis (e.g. FMEA)
- Most importantly…talk to your customers! Understand the consequences and implications when SaMD malfunctions

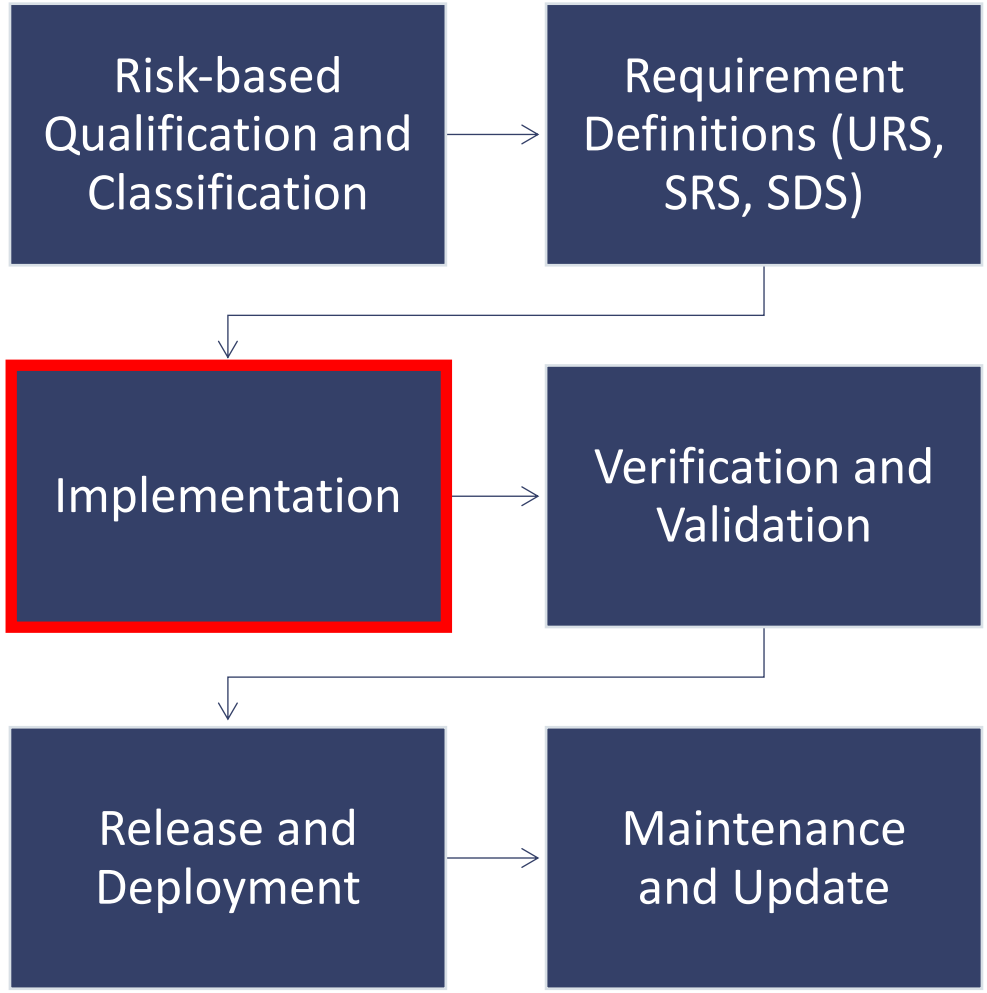
Regulatory Strategy inform software development strategy



Step 2 – Requirement Definitions

- User Requirement Specifications
  - Intend to describe how SaMD integrates with clinical workflow
- Software Requirement Specifications
  - Frontend
  - Backend
  - Risk control measures
  - Non-functional
  - Algorithm performance
  - Data requirements
- Software design Specifications
  - Architecture design decisions based on URS, SRS, and risks.

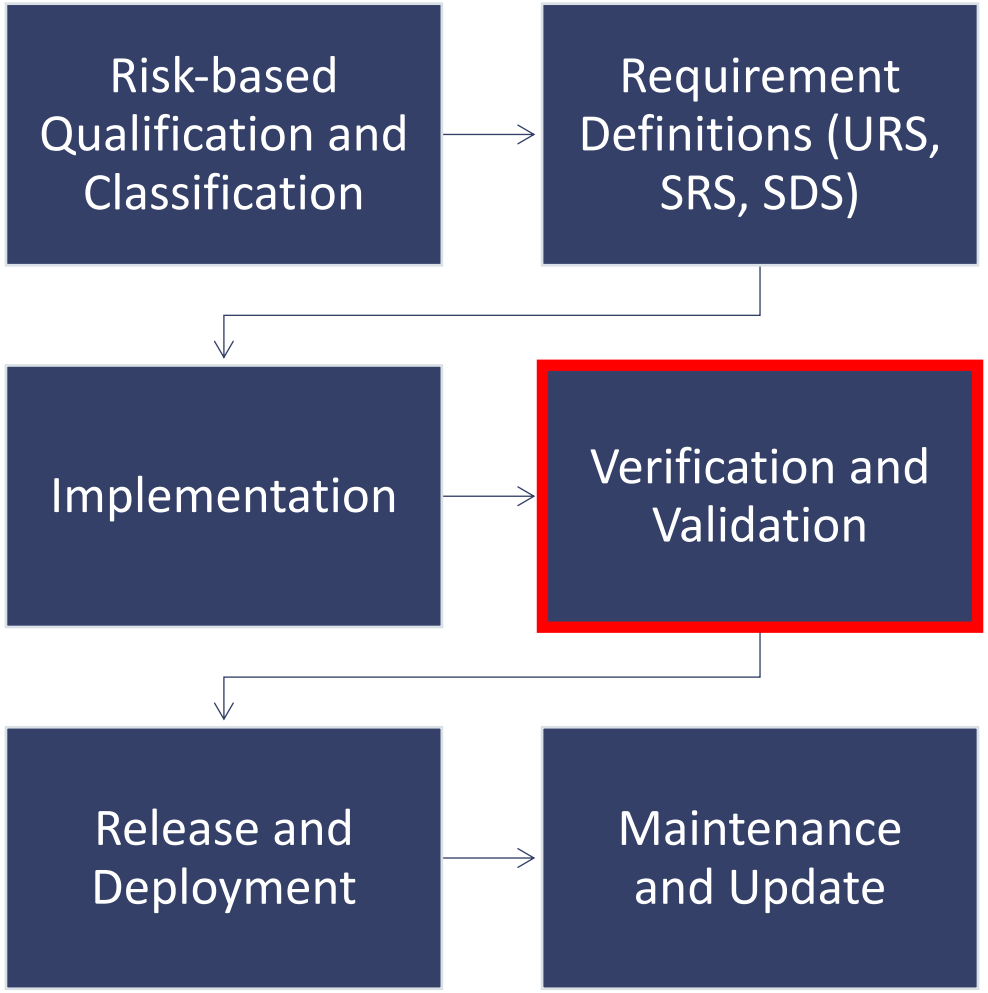
Regulatory Strategy inform software development strategy



Step 3 – Implementation

- Requirement Management
- Change Management
- Github working practice
  - Regression testing
  - Acceptance checklist before release
  - Revision level as audit trail
- Test Management (e.g.
  - Github working practice
  - Regression testing
- Design Reviews
- How to effectively integrate all development tools for design control purposes is key

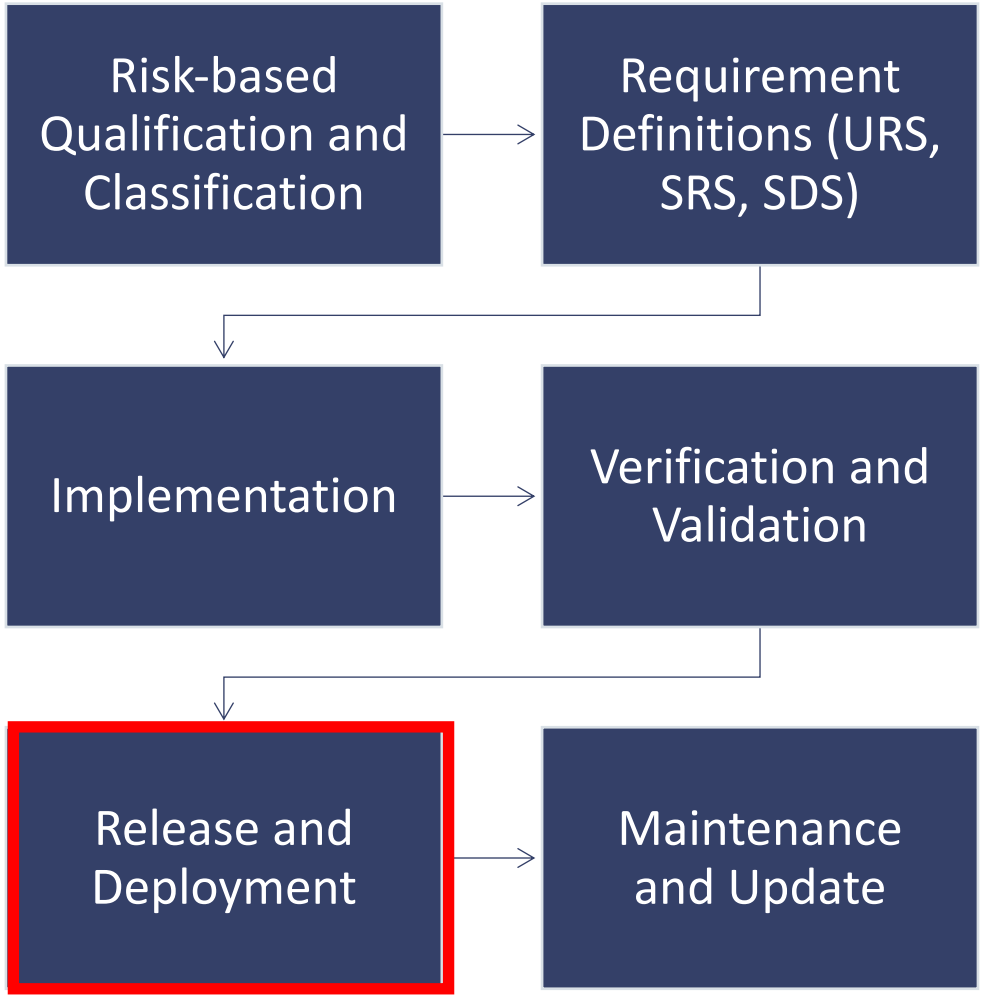
Regulatory Strategy inform software development strategy



Step 4 – V&V

- Verification
  - Test coverage driven by risk profile
  - Boundary conditions and exceptions
  - Impact analysis and regression testing
- Validation
  - Scenarios cover the clinical user and environment
  - Acceptable failure behavior (e.g. specified degraded modes such as fail-safe, fail-secure, fail-soft)

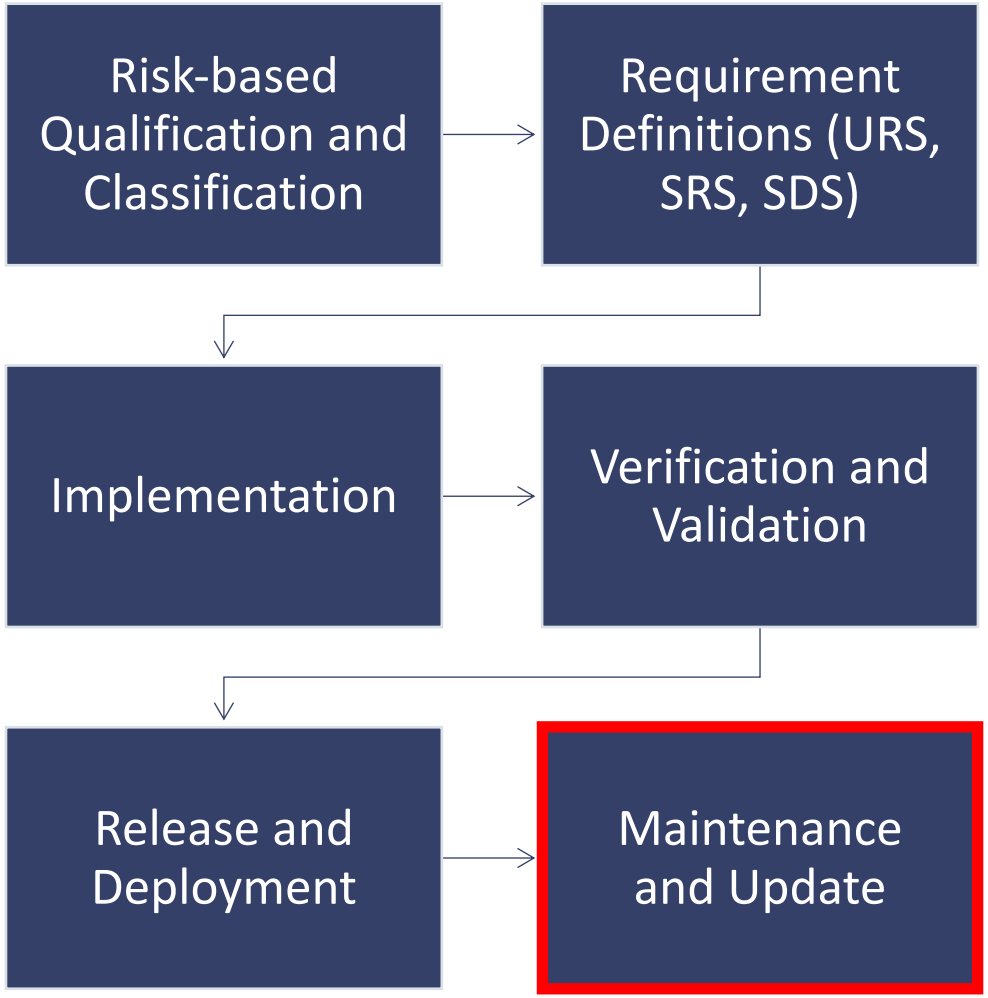
Regulatory Strategy inform software development strategy



Step 5 – Release and Deployment

- Release planning (e.g. checkpoint in version control system)
- Deployment planning
  - Integration with clinical environment (e.g. hospital IT network, human factor, installation/configuration…etc)
- Version identification and control is key audit trail records

Regulatory Strategy inform software development strategy



Step 6 – Maintenance and Update

- Change assessment on safety, effectiveness, and performance
- Feasible for user to safely implement security updates
- Clear steps in instruction for use to guide user update security software, operating system, other systems applications..e.tc

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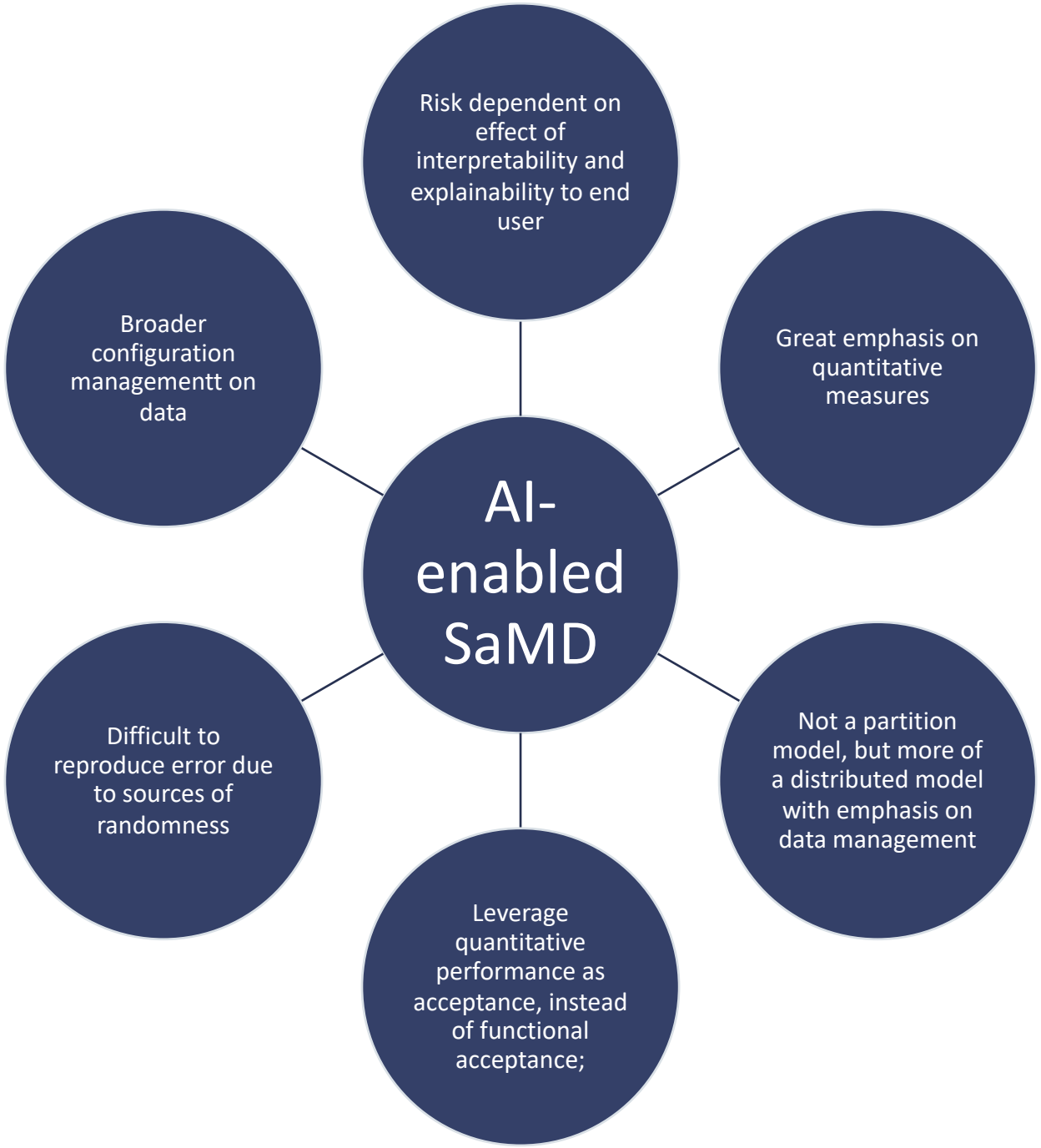
Regulatory Strategy informs SW Development – AI-enabled SaMD


AI-enabled SaMD
Risk dependent on effect of interpretability and explainability to end user
Great emphasis on quantitative measures
Not a partition model, but more of a distributed model with emphasis on data management
Leverage quantitative performance as acceptance, instead of functional acceptance;
Difficult to reproduce error due to sources of randomness
Broader configuration managementt on data

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Recommendations to Manufacturers

How to start?

Organizational-level

SaMD Quality Management Principles

- IEC 62304 SW Lifecycle Management
- Culture of Quality and Organization Excellence (CQOE)
- Pre-Cert program gives appraisal to organization based on CQOR and past experience with software lifecycle management
- Good Machine Learning Practice

Product-level

'Global Approach to SaMD' – IMDRF framework

- SaMD Definition Statement (N10)
- SaMD Risk Categorization (N12)

State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

- SaMD Clinical Evaluation (N41)

What to focus on?

Change control

- Define type of change
- Define “region of potential changes” around the initial specifications and labeling of the original device
- Step-by-step delineation of the data and procedures

Data management

Labeling requirements

Technical assessment in relationship to clinical workflow

- Description of functions
- Define performance specifications
- Intetpretability and explanability

Cybersecurity

- GDPR
- Threat model
- Premarket Information

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What is FDA looking for in premarket submission?

CURRENT

Table 3. Documentation Based on Level of Concern

SOFTWARE DOCUMENTATION	MINOR CONCERN	MODERATE CONCERN	MAJOR CONCERN
Level of Concern	A statement indicating the Level of Concern and a description of the rationale for that level.		
Software Description	A summary overview of the features and software operating environment.		
Device Hazard Analysis	Tabular description of identified hardware and software hazards, including severity assessment and mitigations.		
Software Requirements Specification (SRS)	Summary of functional requirements from SRS.	The complete SRS document.	
Architecture Design Chart	No documentation is necessary in the submission.	Detailed depiction of functional units and software modules. May include state diagrams as well as flow charts.	
Software Design Specification (SDS)	No documentation is necessary in the submission.	Software design specification document.	
Traceability Analysis	Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.		
Software Development Environment Description	No documentation is necessary in the submission.	Summary of software life cycle development plan, including a summary of the configuration management and	Summary of software life cycle development plan. Annotated list of control documents generated during development process. Include the
		maintenance activities.	configuration management and maintenance plan documents.
Verification and Validation Documentation	Software functional test plan, pass / fail criteria, and results.	Description of V&V activities at the unit, integration, and system level. System level test protocol, including pass/fail criteria, and tests results.	Description of V&V activities at the unit, integration, and system level. Unit, integration and system level test protocols, including pass/fail criteria, test report, summary, and tests results.
Revision Level History	Revision history log, including release version number and date.		
Unresolved Anomalies (Bugs or Defects)	No documentation is necessary in the submission.	List of remaining software anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.	

- SOUP and OTS
- Cybersecurity
- Usability

FUTURE (PROPOSED)

Technical Assessment on Quantitative Imaging

SPS

- Potential changes and what type/category (i.e. performance, inputs, intended use).
- The change in risk level associated with each modification.
- Reason for each modification.
- Expected outcome of each modification and the significance/impact.

ACP

- How to evaluate the changes in a way that ensures the performance does not simply improve in certain (targeted) metrics while degrade in others.
- Why the change cannot be achieved now (e.g. if new data expected, why the data cannot be obtained now).
- Evaluation of new data to ensure accuracy/reliability.
- Understanding of what impacts (in addition to performance) a new algorithm would induce.

Upcoming workshop by the FDA – Evolving Role of Artificial Intelligence in Radiological Imaging

DATE: FEB 25-26, 2020

TIME: 8:00AM – 5:30PM ET

- Participants from regulators, industry partners, clinical experts, and academic
- Topics to discuss
  - Emerging Trend in Radiological AI software
  - Risk and Benefits for Radiological AI software
  - FDA's regulatory framework to encourage responsible innovation in AI/ML
  - The Evaluation and Monitoring of AI Algorithms Pre and Post FDA Clearance
  - AI-Guided Image Acquisition: Clinical and Patient Perspectives
  - Regulation of Imaging Devices Containing AI Software

Questions?

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Contact info@rookqs.com for more questions, comments, or to set up a meeting. One of our consultants will be sure to reach out to assist!