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PROXIMA CLINICAL RESEARCH

FINALLY, A NEXT-GEN CRO

Regulatory & Clinical Considerations for SaMD & AI/ML

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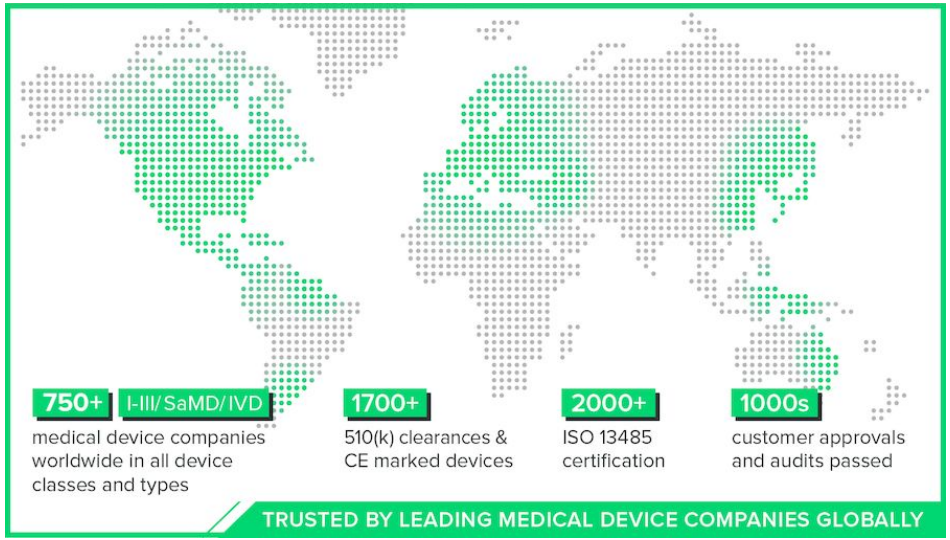

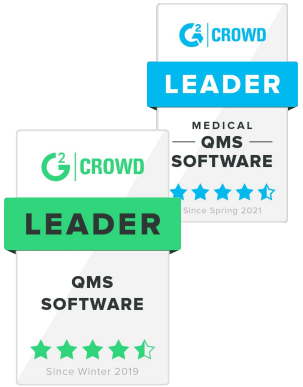

"Best eQMS I have ever used..."

This is the easiest eQMS I have used in the 20 years I have been in the Medical Device Industry. ***It is simple, intuitive and easy to use...*** We are successfully implementing a Quality Culture.

- Director of Regulatory Affairs & Quality Assurance

"Modern QMS Software and Outstanding Customer Service."

★★★★★

"Demystifying QMS and Regulatory Requirements"

★★★★★

"Makes your QMS Simple and Effective"

★★★★★

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Medical Device vs. Wellness Device

A **medical device**:

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, etc. which includes a component part that is:

1. recognized in the official National Formulary/US Pharmacopoeia,
2. intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or
3. intended to affect the structure/function of the body (not through chemical processes)

A **wellness device**:

1. Does not refer to diseases and instead make general claims
2. References specific diseases by:
    a. Helping users reducing risk
    b. Helping users better manage the disease
3. Used for general healthy lifestyle and poses minimal safety risk

Software as a Medical Device (SaMD)

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

SaMD examples

- Software with a medical purpose that operates on a general-purpose computing platform
- Software that is connected to a hardware medical device but is not needed by that hardware medical device to achieve its intended medical purpose is SaMD and not an accessory to the hardware medical device

Non-SaMD examples

- Software that is used to drive pumps and motors of a medical device
- Software that forms a closed loop of a medical device
- Hospital tech- scheduling, workflow, etc
- Software that monitors performance functioning

Intended Use/ Indications for Use

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Intended Use:

General purpose of the device or its function

Indications for Use:

Describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, and the patient population

Determining Intended Use:

Based upon proposed labeling, grounded in safety and effectiveness of the device

Change in Indications of Use → New Intended Use:

If change in indications of use affect safety or effectiveness, new intended use is needed. Changes include:

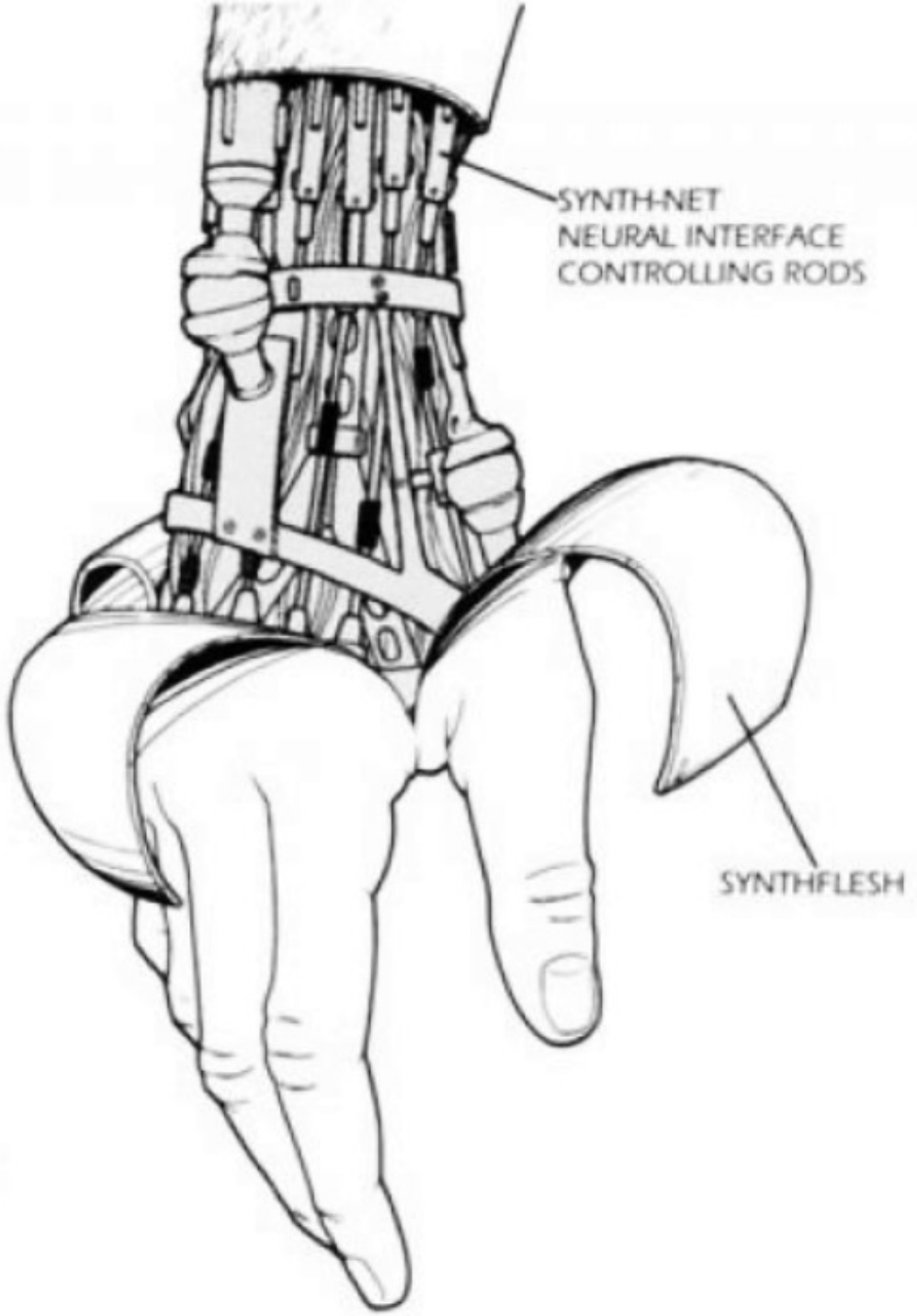
- Diagnostic to screening indication
- Anatomical structure of use
- Patient population
- Clinical context or setting

Creating an Intended Use Statement

The **[INSERT DEVICE NAME]** is a **[INSERT WHAT IT IS]** that **[INSERT WHAT IT IS USED FOR].**

Creating an Intended Use Statement

- **Synthflesh** is a **polymer based synthetic skin** that **fuses cuts and protects organic internal muscles, tissues, or synthetic components, such as controlling rods.**

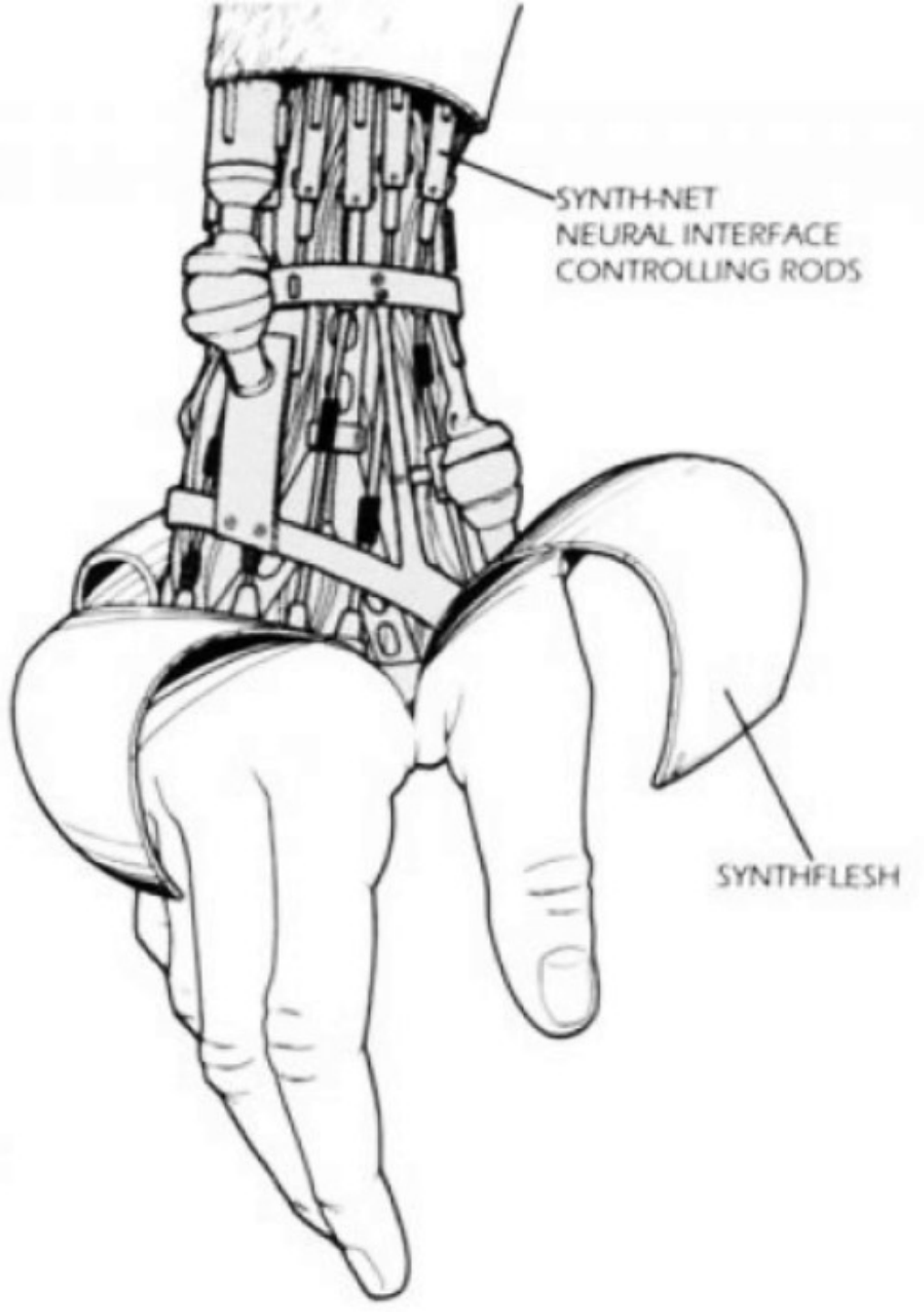


Creating an Indications for Use Statement

The **[INSERT DEVICE NAME]** is a **[INSERT WHAT IT IS]** that **[INSERT WHAT IT IS USED FOR] in [INSERT LOCATION] by [USERS] for [INSERT PATIENT POPULATION].**

Creating an Intended Use Statement

- **Synthflesh** is a **polymer based synthetic skin** that **fuses cuts and protects organic internal muscles, tissues, or synthetic components, such as controlling rods in patients whose father cut off their hand.**



510(k) Number *(if known)*
K203514

Device Name

Precise Position

Indications for Use *(Describe)*

The Precise Position is intended for use with Philips Incisive CT systems. The device provides the following guided workflow.

- Patient orientation identification
- Surview range recommendation
- Automatic centering the patient anatomy
- Provide visual images of patient on the table

Precise position is indicated for use for CT imaging of the head, chest, abdomen, pelvis, and combination of those anatomies.

Patient population limitation: Patient younger than 16 years are not supported.

A real example

SaMDs are used in a few different ways.

Treat or Diagnose Diseases

By connecting to other devices and/or providing a therapy

Drive Clinical Management

Enhancing current treatment by providing safety, providing risk analysis for a condition, or identifying early signs of a disease

Inform Clinical Management

To present information or inform of options

There are certain factors that can lower or rise the propensity for harm to occur.

- The type of disease or condition
- Fragility of the patient with respect to the disease or condition
- Progression of the disease or the stage of the disease/condition
- Usability of the application
- Designed towards a specific user type
- Level of dependence or reliance by the user upon the output information
- Ability of the user to detect an erroneous output information
- Transparency of the inputs, outputs and methods to the user
- Level of clinical evidence available and the confidence on the evidence
- The type of output information and the level of influence on the clinical intervention
- Complexity of the clinical model used to derive the output information
- Known specificity of the output information
- Maturity of clinical basis of the software and confidence in the output
- Benefit of the output information vs. baseline.
- Technological characteristics of the platform the software are intended to operate on
- Method of distribution of the software

There are certain factors that can lower or rise the propensity for harm to occur.

- Significance of the output to the healthcare condition or situation
- Seriousness of the condition or situation

SaMD Categories

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

IEC 62304 Safety Classification is assigned A, B, or C depending on the risk to the patient, operator, or other user.

A

- The software CANNOT contribute to a hazardous situation
- The software CAN contribute to a hazardous situation BUT it is at an acceptable level after risk controls are put in place.

B

- The software CAN contribute to a hazardous situation which results in unacceptable risk after consideration of external risk control measures and the resulting possible harm is non-serious.

C

- The software CAN contribute to a hazardous situation which results in unacceptable risk after consideration of external risk control measures to the and the resulting possible harm is death or serious injury

FDA currently uses Level of Concern- Major, Moderate, or Minor.

Major	• Blood establishment computer software • Used in combination with drug or biologic • Accessory to a medical device that is a major level of concern • Could result in serious injury or death
Moderate	• Not any of the above • Accessory to a medical device that is a moderate level of concern • Malfunction or latent flaw leads to delay in care or diagnosis that can lead to injury
Minor	• None of the above applies

Documentation required for the pre-market submission depends on the level of concern.

Software Description	• All levels of concern	• Includes programming language, hardware platform, operating system, and off-the-shelf software, if applicable
Device Hazard Analysis	• All levels of concern	• Typically includes hardware and software • Tabular format • Includes severity and mitigations
Software Requirement Specifications	• Major • Moderate • Func. Summ-Minor	• Includes functional, performance, interface, design, developmental, and other requirements
Architecture design chart	• Major • Moderate	• Flowchart • Includes relationships among the major functional units, including relationships to hardware and to data flows such as networking

Documentation required for the pre-market submission depends on the level of concern.

Software Design Specs	• Major • Moderate	• Enough detail to ensure that the work performed by the software engineers was clear and unambiguous, with minimal ad hoc design decisions
Traceability analysis	• All levels of concern	• Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing
Software Design Environment	• Major • Moderate	• Software development life cycle plan • Configuration or change management plan

Documentation required for the pre-market submission depends on the level of concern.

V&V	• All levels of concern	• Minor: summary of pass/fail criteria and test results for system or device level • Moderate: Summary list of V&V and pass/fail criteria with results • Major: Same as moderate and any failed results/ modifications
Revision Level History	• All levels of concern	• History of software revision • List of versions
Unresolved anomalies	• Major • Moderate	• Problem • Impact on device performance • Any plans or timeframes for correcting the problem (where appropriate).

HOLD THE PHONE!

FDA Put out a Draft Guidance changing the documentation levels.

Enhanced

- Blood establishment computer software
- Used in combination with drug or biologic
- Classified as class III
- Could result in serious injury or death

Basic

- None of the above

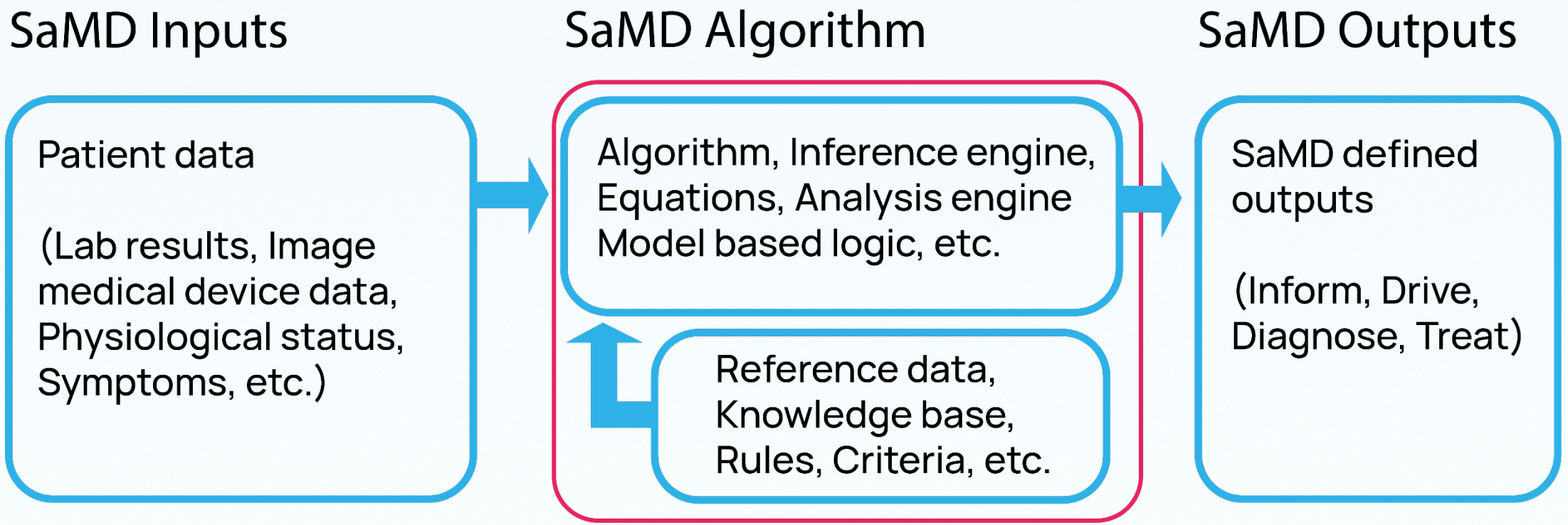
What changes with the documentation?

Here are a few key differences

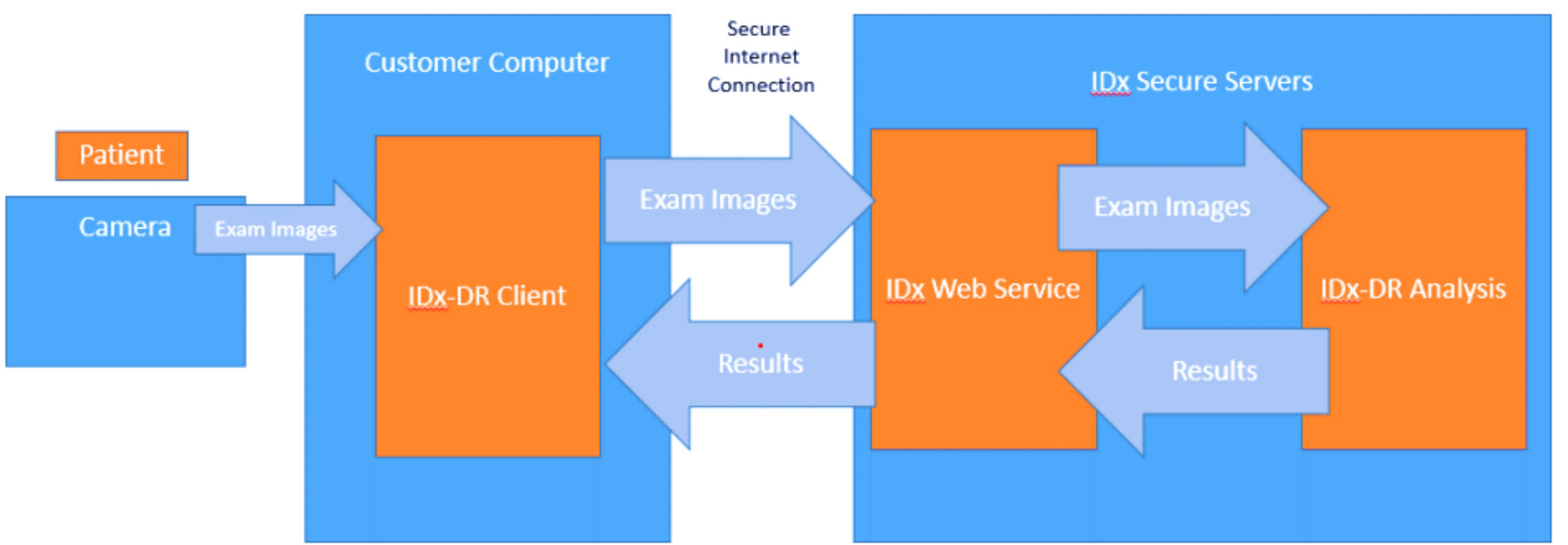
1. Risk management file
2. Both categories will need full SRS
3. Both categories will need software architecture
4. Software development and maintenance
5. Both categories will need unresolved anomalies

CLINICAL CONSIDERATIONS

Software as a Medical Device is software that uses an algorithm that operates on Data Input to generate an output intended for medical use.



IDx-DR is indicated for use by healthcare providers to automatically detect more than mild diabetic retinopathy in adults diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy.

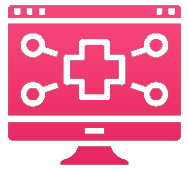


What would the flowchart for a Tricorder look like?

The clinical evaluation process involves analyzing three different areas.

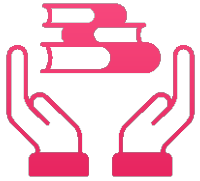
1	**VALID CLINICAL ASSOCIATION**	Is there a valid clinical association between your SaMD output and your SaMD's targeted clinical condition?
2	**ANALYTICAL VALIDATION**	Does your SaMD correctly process input data to generate accurate, reliable, and precise output data?
3	**CLINICAL VALIDATION**	Does use of your SaMD's accurate, reliable, and precise output data achieve your intended purpose in your target population in the context of clinical care?

Valid clinical association is the extent to which the SaMD'S output is clinically accepted or well-founded.



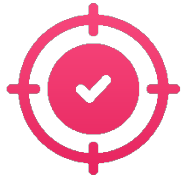
- Is my technology founded in well-established clinical principles?

- Are my outputs clinically meaningful?



- Do I have literature, professional guidelines, or clinical trials to support the clinical association?

Analytical validation confirms that the software was properly constructed.



- Are the outputs of my modules accurate, reliable and precise?

- Does the software meet user needs specifications and technical specifications?

- Do you have data as part of the QMS V&V testing or through previously collected data?

Clinical validation means the output results in a meaningful, measurable, patient-relevant clinical outcome.

- Are there studies with the same intended use or with a different intended use where extrapolation can be justified?

- Have you generated new clinical data for a specific intended use?

Artificial Intelligence & Machine Learning

Artificial intelligence:

- Science and engineering of making intelligent machines, especially intelligent computer programs
- Different techniques, including models based on statistical analysis of data, expert systems that primarily rely on if-then statements, and machine learning

Machine Learning:

- Can be used to design and train software algorithms to learn from and act on data
- ‘Locked’ so that its function does not change, or ‘adaptive’ so its behavior can change over time based on new data

Following concepts of good machine learning practices will ensure appropriate clinical validation of all SaMD.

Key Principles of Good Machine Learning Practice (GMLP)

1	**Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle**	Understand the clinical workflow and where and how the software fits into the current paradigm.
2	**Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population**	The datasets need to be generalizable and include all relevant and important factors of the patient demographics and algorithm inputs.
3	**Training Data Sets Are Independent of Test Sets**	Datasets used to train the algorithm must be separate from the datasets used to validate to reduce bias in the algorithm's performance.

Following concepts of good machine learning practices will ensure appropriate clinical validation of all SaMD.

Key Principles of Good Machine Learning Practice (GMLP)

4	**Selected Reference Datasets Are Based Upon Best Available Method**	Datasets used should be appropriately characterized for their intended use
5	**Testing Demonstrates Device Performance during Clinically Relevant Conditions**	The technology should be used in the intended use case by the intended users in the intended use environment.
6	**Deployed Models Are Monitored for Performance and Re-training Risks are Managed**	The software should be monitored over its lifecycle to see if performance is holding up to the clinical data generated during development. Re-training efforts should be verified to not negatively affect performance.

Sometimes data can't be generated in support of 1, 2, and 3.

If that is the case for you, try the following:

- Modify your intended use
- Make changes to the software
- Change the patient population or target clinical association
- Gather and perform more data analysis

Last year FDA released the artificial intelligence/machine learning (AI/ML)-based software as a medical device (SAMD) action plan.

Predetermined Change Control Draft Guidance

Incomplete FY 2022, resources permitting

Encourage Good Machine Learning Practice

Published GMLP Principles in October 2021

Ensuring appropriate labeling to end users

Compiling data form 2020 PEAC for workshop

Regulatory Research Methods

Working with universities and established internal FDA AI group

Real world performance data

Work with companies on voluntary basis on building a framework for evidence collection for real-world

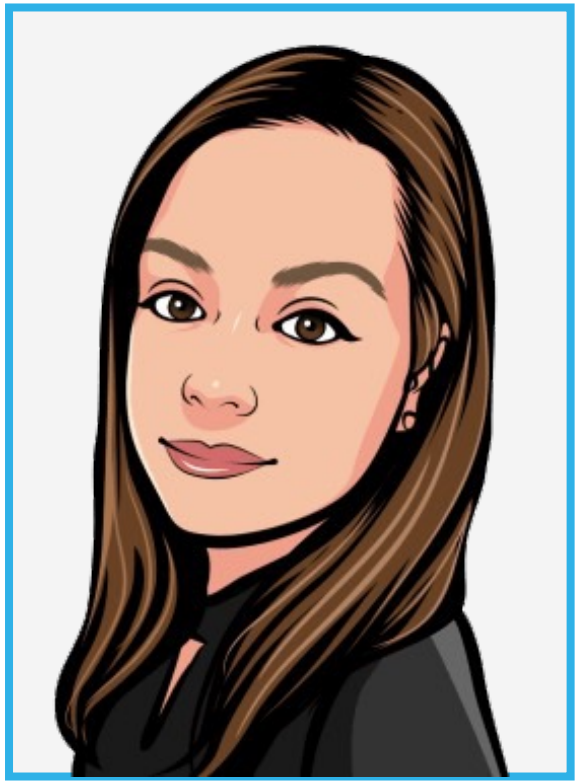
Post-market surveillance

Capture customer issues through the following:

- *Complaints*
- *Market studies*
- *Focus groups*
- *General inquiries*

…also set up the device to detect any errors or failures.

Let's Connect!



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