IMDRF International Medical Device Regulators Forum

Software as a Medical Device (SaMD)

Clinical Evaluation

IMDRF/SaMD WG (WD2)/N41R1: 2016

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Chair – SaMD Working Group

NWIE Proposal - Software as a Medical Device (SaMD): Clinical Evaluation

Scope

Guidance on when clinical data may be needed for an original SaMD and for a modification to a SaMD based on the risk classification for SaMD (SaMD N12) adopted by IMDRF to support market authorization.

Rationale

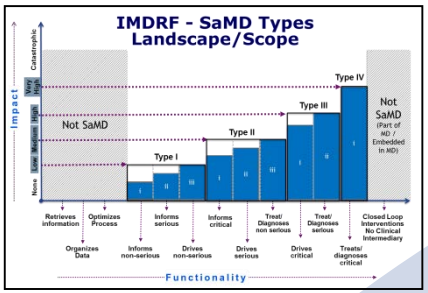
Though current clinical guidance are intended to be relevant across a broad spectrum of technology, SaMD operates in a complex socio-technical environment heavily influenced by the inherent nature of software that enables a highly interactive and iterative technological environment. A majority of the respondents (from the IMDRF survey) either believe current clinical guidance needs to be revised with criteria specific for SaMD, or don't know whether it applies to SaMD.

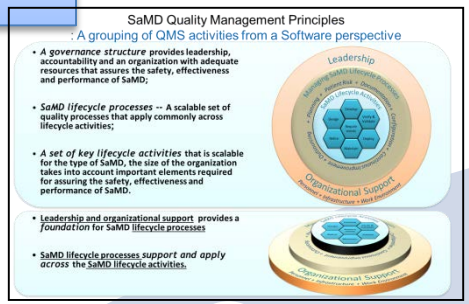
Alignment with Goals/Objectives

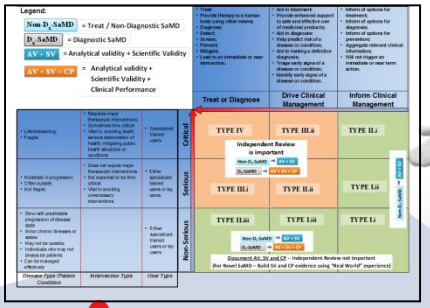
A common understanding on the application of clinical evaluation and clinical evidence processes and the need for clinical data to support market authorization will lead to increased transparency and promoting a converged thinking on this topic.

IMDRF International Medical Device Regulators Forum

On a Path towards global convergence





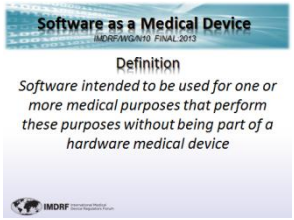


2015 – QMS control ➔Translating Software development practices to regulatory QMS

SaMD – Application of clinical Evaluation

On target for Final March 2017

2014 – Risk framework based on impact to patients



2013 Foundational vocabulary

Key Assumptions for Work Item

- All manufacturers of SaMD follow adequate quality management systems
- Quality Management Systems ensures
  - Rigor in generating evidence towards
    - *Usability*
    - *Quality – (conformance to specifications, "fitness for use" and free from defects)*
    - *Reliability*
  - Service and Continuous Improvement - Ability to maintain quality while in use.
- SaMD quality validation is covered as part of QMS
- Except in small cases almost all SaMD generate information for use and reliance
- All SaMD require some clinical evaluation method to assure effectiveness and clinical benefit
- Clinical evaluation scope is dependent on "intended use" as defined by the manufacturer of SaMD

Relationship to Previous Documents

	SaMD mfg 1	SaMD mfg 2	SaMD mfg 3	SaMD mfg ..	SaMD mfg ..	SaMD mfg n
Type I	X		X	X		
Type II		X		X		
Type III	X		X			X
Type IV				X	X	

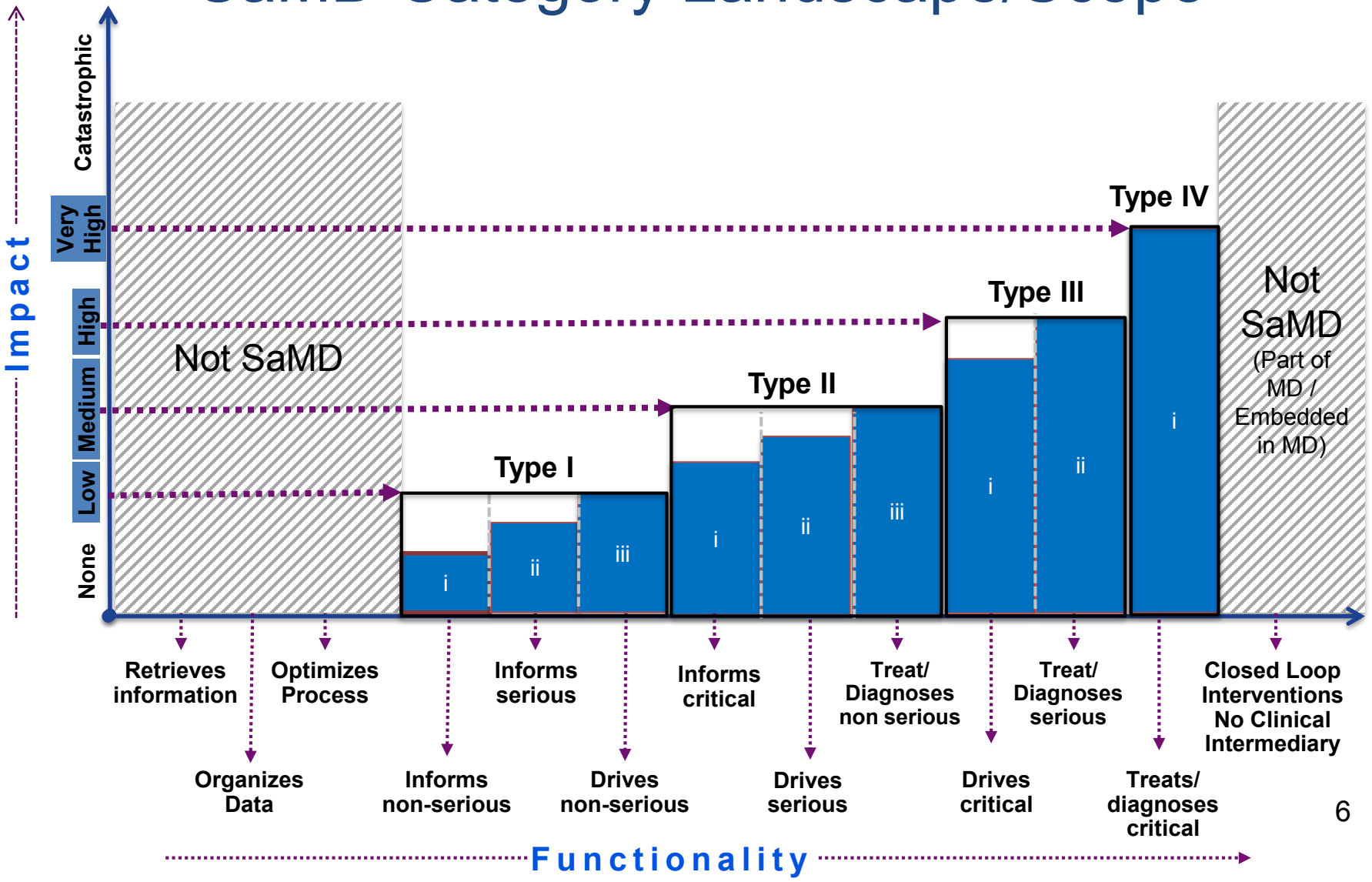
Common SaMD Category specific expectations: (**Based on Patient impact**
- when and which methods and processes are important to independently verify?
- How much / what type evidence is adequate to verify?)

- QMS Process
- Risk management
- Engineering validation
- Clinical evaluation and evidence

Common SaMD manufacturer expectations (methods and processes that each mfg should have **regardless of type of SaMD made**) :
- N12- identification of SaMD in risk framework
- N23- Quality management system – 13485
- Risk management system – ISO I4971
- Process for evaluation of safety, effectiveness and performance, including clinical evaluation

New work item:
Software as a Medical Device (SaMD): Clinical Evaluation

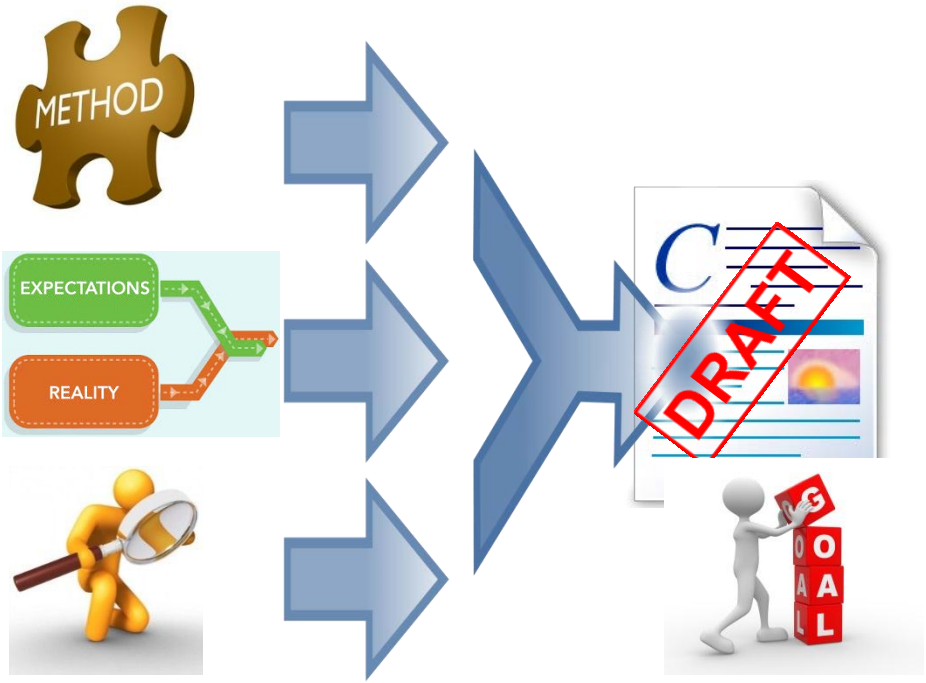
SaMD Category Landscape/Scope



Goal

International Guidance -- Based on "SaMD type" (level of impact on public health) and unique aspects of software

- Relevant clinical evaluation methods and processes which can be appropriately used for SaMD to generate clinical evidence
- The necessary level of clinical evidence for different categories of SaMD
- SaMD categories where independent review is important or not important



Current Challenges

Expectations / importance by SaMD category

- Current GHTF / Regulatory does not easily translate to new entrants (SaMD Manufacturer)
- Clinical evaluation current expectations time frame – misalignment with development cycle times for SaMD
- Disparate vocabulary on what is considered clinical evaluation
- Relationship between QMS validation and clinical evaluation is unclear

How much and what level of evidence is adequate

- Reuse of predicate clinical evidence (same or different manufacturer) is unclear
- Too many confounding factors during implementation, i.e., risk management, change, clinical evaluation, technical validation, etc.

Which method to use?

- SaMD can use any inputs and it is hard to control in clinical evaluation – as typically expected in MD/IVD
- SaMD enables Novel outcomes that do not necessarily have Gold Standards
- SaMD changes constantly -> SW is learning – not static as MD/IVD

Desired State – WG summary

- Promote an Agile / learning clinical evaluation framework
- For continuously changing SaMD – need:
  - Ability to update Clinical Evidence continuously
  - Leverage the capability of learning new evidence
  - Allow self-learning
- Allow postmarket continuous evaluation paradigm (real world performance)
- Promote technology capabilities to facilitate collecting & learning real world clinical evidence
- Allow SaMD outcomes to evolve in claims and functionality as postmarket evidence is being collected.
- Pre-market clinical evidence may be different for SaMD, requiring methods that allow postmarket collection

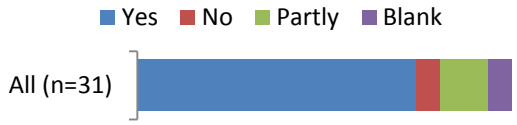
General Feedback and Early Buy-in Prior to Draft Proposal Helps Solidify Key Concepts

- Specific feedback on alignment to objective
  - Clarity
  - Message
  - Scope
  - Audience
  - Tone
- Solicit examples to illustrate document concepts
- Solicit editorial feedback on current content

- Comments from WG and extended network of internal and external stakeholders
- Broad global cross-section of respondents:
  - 8 Global Regulators (ANVISA, CFDA, EU - Germany Federal Ministry of Health, Sweden MPAFDA, HC, HSA, TGA, PMDA, USFDA)
  - 10 Trade Associations & Members
  - 3 Academia
  - 6 Other (research, software industry)
- 100+ “alignment to objective” comments
- 500+ “content” comments

Key Points for Improvement

Does the document convey the rationale for why clinical evaluation is needed?



- Suggestions to be more direct

Does the document adequately explain the concepts?

- IVD Concepts don't easily translate ;
- Need examples
- Provide readers context from previous SaMD docs

Does the document adequately translate GHTF, MD, IVD guidance

- IVD translation not ideal

Does the document appropriately translate and apply current clinical vocabulary for SaMD?

- not all IVD terms/concepts apply to SaMD
- Use of IVD terms doesn't differentiate uniqueness of SaMD
- V&V confusing with clinical eval

Does the document clearly explain what is expected for clinical evaluation for SaMD?

- What makes SaMD unique?
- Lacks clarity for why clinical evaluation for SaMD needs separate discussion

Does the document cover the intention captured in the introduction or vice-a versa?

- Document seems to relate mainly to diagnostic SaMDs

Is there clarity that the document is a continuum to prior IMDRF document?

- Unclear if continuum of previous IMDRF concepts? Show relationship to previous documents

Document Highlights

- Clinical evidence recommendations tailored for non-diagnostic, therapeutic functionality and diagnostic SaMD.
  - Higher risk novel SaMD (categories II.ii, III and IV) should generate appropriate association of the SaMD output to the clinical condition/physiological state
  - Higher risk diagnostic SaMD (categories II.ii, III and IV) should generate appropriate clinical performance evidence (in addition to scientific validity and analytical validity)

- Recommendation for Higher risk SaMD to have "independent review"

Key Concepts

Clinical Evaluation (CE)

Analytical Validity

- Accuracy
- Precision
- Limit of detection
- Linearity or associated transfer function
- Analytical sensitivity

Clinical Validity

Scientific Validity

Scientific validity is the association of the SaMD output to a clinical condition/physiological state.

Clinical Performance

- Sensitivity
- Specificity;
- ROC curve
- Positive predictive value
- Negative predictive value
- Likelihood ratio
- Cut-off thresholds, indices or scales

Clinical Evaluation & Evidence

Clinical Evaluation (CE)

- Analytical Validity
- \+
- Clinical Validity
  - Scientific Validity + Clinical Performance

Non-D_x-SaMD

Clinical Evaluation (CE)

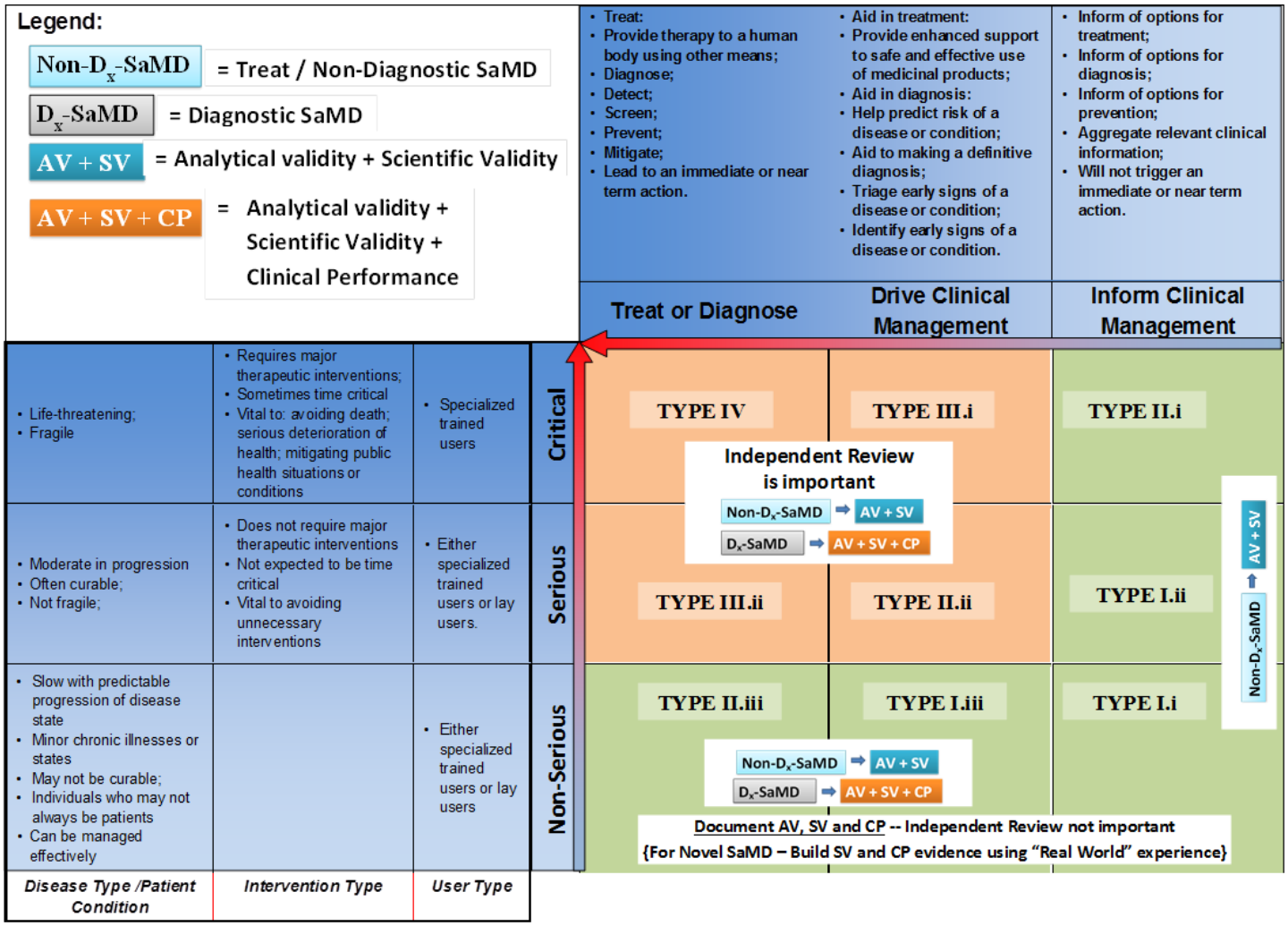
- Analytical Validity
- \+
- Clinical Validity
  - Scientific Validity

D_x-SaMD

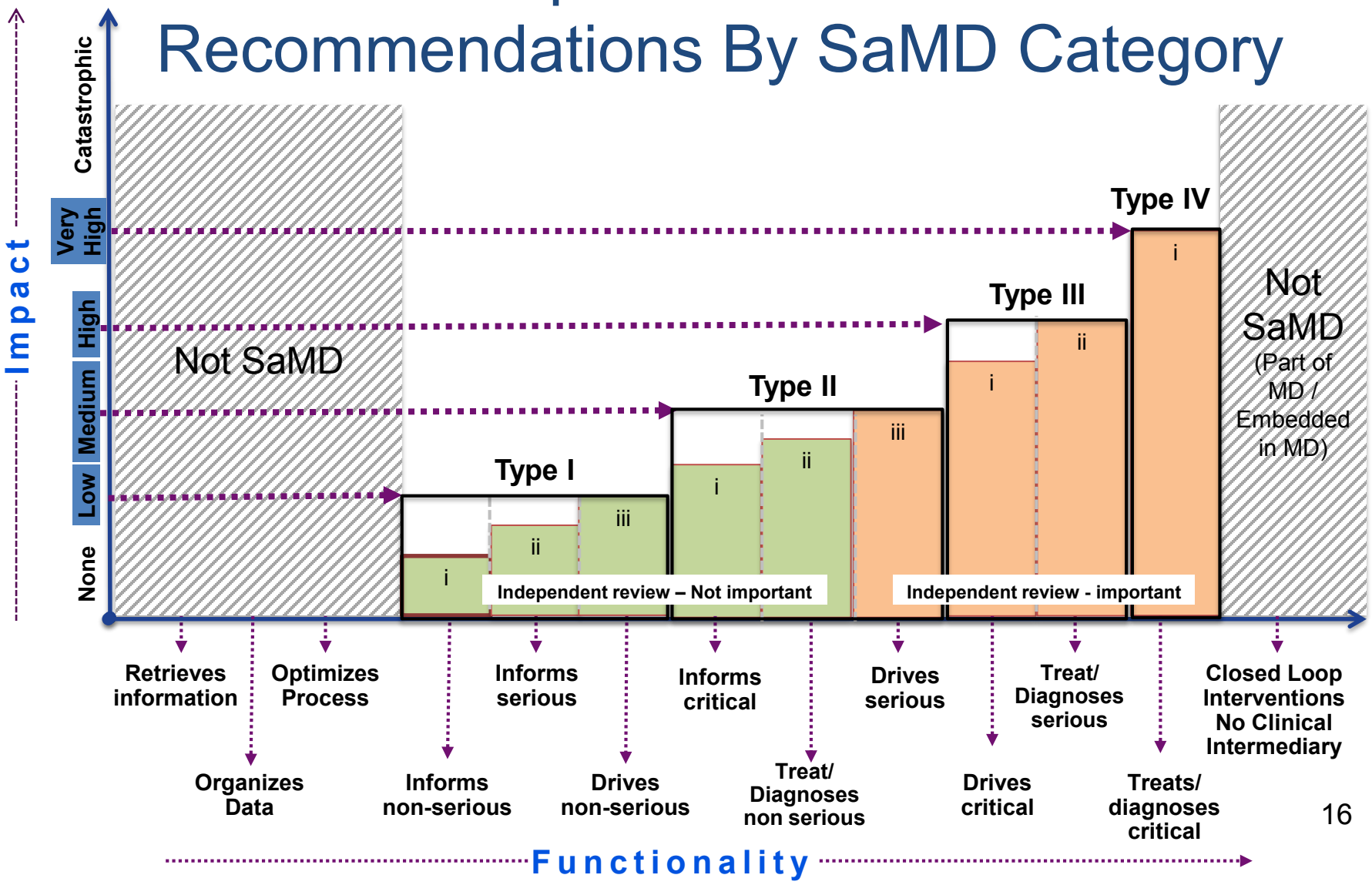
Clinical Evaluation (CE)

- Analytical Validity
- \+
- Clinical Validity
  - Scientific Validity + Clinical Performance

Recommended Framework for SaMD Clinical Evaluation Intrinsically Linked to Prior SaMD Guidances



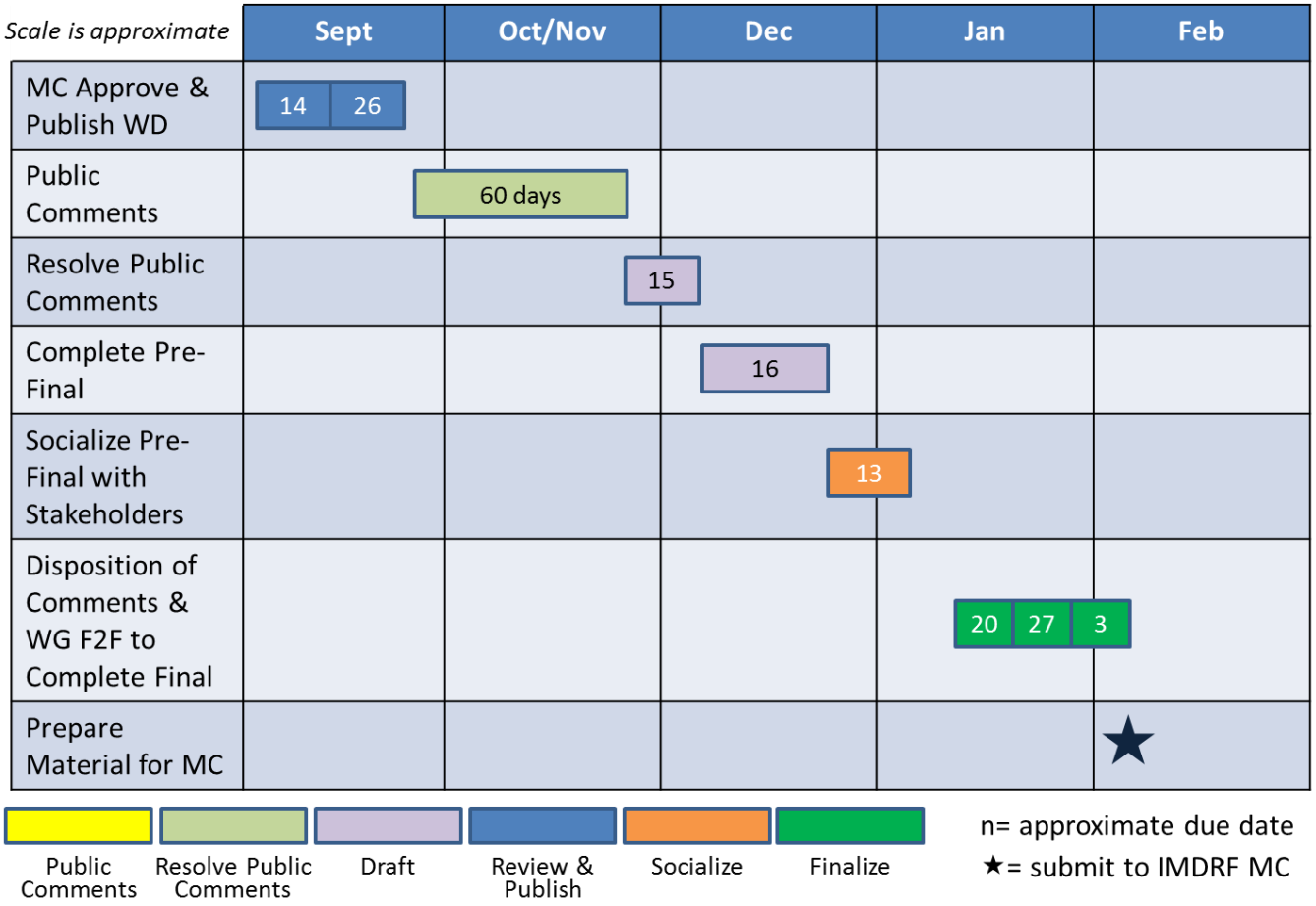
Independent Review Recommendations By SaMD Category



Public Consultation – Targeted Questions

High level feedback	Yes/No	Comment and rationale and proposed recommendations
Does the document address the intention captured in the introduction/scope or vice-a versa?		
Does the document appropriately translate and apply current clinical vocabulary for SaMD?		
Are there other types of SaMD beyond those intended for non-diagnostic, diagnostic and therapeutic purposes that should be highlighted/considered in the document?		
Does the document adequately address the relevant clinical evaluation methods and processes for SaMD to generate clinical evidence?		
Are there other appropriate methods for generating clinical evaluation evidence that are relevant for SaMD beyond those described in the document?		
Are the recommendation identified in section 7.2 related to the" importance of clinical evaluation evidence" appropriate as outlined for the different SaMD categories ?		
Are the recommendation identified in section 7.3 related to the" importance of independent review " appropriate as outlined for the different SaMD categories ?		
Given the uniqueness of SaMD and the proposed framework -- is there any impact on currently regulated devices or any possible adverse consequences?		

Final Document Project Plan



Special thanks to all working group members and stakeholders for engaging and providing valuable input towards N41/WD