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.
On a Path towards global convergence

2013
Foundationa l vocabulary

2014 – Risk framework based on impact to patients

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

SaMD – Application of clinical Evaluation
On target for Final March 2017

SaMD Quality Management Principles
- A governance structure provides leadership, accountability, and resources that ensure the safety, effectiveness, and performance of SaMD.
- SaMD lifecycle processes – A suite of quality processes that apply consistently across lifecycle activities.
- A set of key lifecycle activities that is suitable for the type of SaMD. The set of activities for the organization takes into account important elements required for demonstrating the safety, effectiveness, and performance of SaMD.
- Responsibility and organizational support defines the foundation for SaMD lifecycle activities.

SaMD, Software as a Medical Device
Definition
Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device

IMDRF - SaMD Types Landscape/Scope

SaMD

IMDRF International Medical Device Regulators Forum
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

<table>
<thead>
<tr>
<th>Type</th>
<th>SaMD mfg 1</th>
<th>SaMD mfg 2</th>
<th>SaMD mfg 3</th>
<th>SaMD mfg 4</th>
<th>SaMD mfg n</th>
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<td>Type II</td>
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<tr>
<td>Type IV</td>
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</table>

### 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 14971
  - Process for evaluation of safety, effectiveness and performance, including clinical evaluation

### 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

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

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

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

Clinical Performance
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 + Clinical Performance

$D_x$-SaMD

Clinical Evaluation (CE)

Analytical Validity + Clinical Validity

Scientific Validity + Clinical Performance
Recommended Framework for SaMD Clinical Evaluation
Intrinsically Linked to Prior SaMD Guidances

Legend:
- **Non-D<sub>x</sub>-SaMD** = Treat / Non-Diagnostic SaMD
- **D<sub>x</sub>-SaMD** = Diagnostic SaMD
- **AV + SV** = Analytical validity + Scientific Validity
- **AV + SV + CP** = Analytical validity + Scientific Validity + Clinical Performance

<table>
<thead>
<tr>
<th>Disease Type/Patient Condition</th>
<th>Intervention Type</th>
<th>User Type</th>
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</thead>
<tbody>
<tr>
<td>Treat or Diagnose</td>
<td>Drive Clinical Management</td>
<td>Inform Clinical Management</td>
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<tr>
<td>Treat</td>
<td>• Provide therapy to a human body using other means; • Aid in treatment: • Inform of options for treatment;</td>
<td>• Provide enhanced support to safe and effective use of medicinal products; • Help predict risk of a disease or condition; • Inform of options for prevention; • Aggregate relevant clinical information; • Will not trigger an immediate or near term action.</td>
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<td>Detect</td>
<td>• Detect; • Prevent; • Mitigate; • Lead to an immediate or near term action.</td>
<td>• Detect; • Prevent; • Mitigate; • Lead to an immediate or near term action.</td>
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<tr>
<td>Screen; Prevent; Mitigate;</td>
<td>• Treat; • Provide therapy to a human body using other means; • Aid in treatment: • Inform of options for treatment;</td>
<td>• Detect; • Prevent; • Mitigate; • Lead to an immediate or near term action.</td>
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<tr>
<td>Triage early signs of a</td>
<td>• Detect; • Provide enhanced support to safe and effective use of medicinal products; • Help predict risk of a disease or condition;</td>
<td>• Inform of options for prevention; • Aggregate relevant clinical information; • Will not trigger an immediate or near term action.</td>
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<td>disease or condition;</td>
<td>• Aid in diagnosis:</td>
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<tr>
<td>Identify early signs of a</td>
<td>• Aid to making a definitive diagnosis;</td>
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<tr>
<td>disease or condition.</td>
<td>• Triage early signs of a disease or condition;</td>
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</tbody>
</table>

Critical
- Type IV
- Independent Review is important
- Non-D<sub>x</sub>-SaMD = AV + SV
- D<sub>x</sub>-SaMD = AV + SV + CP

Serious
- Type III.i
- Non-D<sub>x</sub>-SaMD = AV + SV

Non-Serious
- Type II.i
- Document AV, SV and CP -- Independent Review not important
- {For Novel SaMD -- Build SV and CP evidence using “Real World” experience}

Legend:
- Life-threatening; Fragile
- Moderate in progression; Often curable; Not fragile
- Slow with predictable progression of disease state; Minor chronic illnesses or states; May not be curable; Individuals who may not always be patients; Can be managed effectively
Independent Review
Recommendations By SaMD Category

- Type I: Independent review – Not important
- Type II: Independent review - important
- Type III: Not SaMD (Part of MD / Embedded in MD)
- Type IV: Closed Loop Interventions No Clinical Intermediary

Functionality:
- Retrives information
- Optimizes Process
- Informs non-serious
- Drives non-serious
- Informs critical
- Drives critical
- Treat/Diagnoses non-serious
- Treat/Diagnoses critical

Impact:
- None
- Low
- Medium
- High
- Very High
- Catastrophic

Impact and Functionality:
- Type I: Independent review – Not important
- Type II: Independent review - important
- Type III: Not SaMD (Part of MD / Embedded in MD)
- Type IV: Closed Loop Interventions No Clinical Intermediary
### Public Consultation – Targeted Questions

<table>
<thead>
<tr>
<th>High level feedback</th>
<th>Yes/No</th>
<th>Comment and rationale and proposed recommendations</th>
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<td>Does the document address the intention captured in the introduction/scope or vice-a versa?</td>
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<td>Are there other types of SaMD beyond those intended for non-diagnostic, diagnostic and therapeutic purposes that should be highlighted/considered in the document?</td>
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<td>Given the uniqueness of SaMD and the proposed framework -- is there any impact on currently regulated devices or any possible adverse consequences?</td>
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## Final Document Project Plan

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- Public Comments
- Resolve Public Comments
- Draft
- Review & Publish
- Socialize
- Finalize

n = approximate due date
★ = submit to IMDRF MC
Special thanks to all working group members and stakeholders for engaging and providing valuable input towards N41/WD