Navigating the Challenges of Digital Health Innovation

Moderator: Adam Saltman – Medical Officer, Clinical & Scientific Policy, OPEQ IO, CDRH/FDA
Matthew Diamond – Medical Officer, Digital Health, OSPTI, CDRH/FDA
Rama Pidaparti – Medical Devices & Life Sciences, L&T Technology Services
Bernhard Kappe – Founder and CEO, Orthogonal
Barbara Fant – President and Principal Regulatory Consultant, Clinical Research Consultants, Inc.
Hylton Kalvaria – Verana Health
Why Are We Talking About Digital Health?

Uncharted Territory

Fear of the Unknown
No Map
Hidden Traps and Obstacles
Poisonous Creatures
Why Are We Talking About Digital Health?

Uncharted Territory

Fear of the Unknown
No Map
Hidden Traps and Obstacles
New, Very High Mountain
Why Are We Talking About Digital Health?

You need:

A dictionary
A map
A experienced guide
Bug spray and long pants
Mountaineering gear
Agenda

• Background and glossary
• FDA’s latest thinking – Digital health, Pre-Cert, AI/ML in SaMD
• Challenges specific to DH apps: RWE, AI, ML, Compliance, ...
• Building in quality
• Regulatory issues/guidelines/requirements
• Learn from learners and experts
• Panel discussion and audience questions
Speakers

• Matthew Diamond, MD, PhD
  • FDA – Senior clinical expert for digital health medical devices; Team leader for developing policy on emerging technologies in digital health
  • Rehabilitation and Sports Medicine physician on faculty at NYU/ Rusk Institute
  • Chief Medical Officer, Nokia (previous position)
  • Medical Director at Fossil Group and Misfit Wearables (previous positions)
  • Vice Chair, Consumer Technology Association (CTA) Health & Fitness Technology Board and Founder, Health & Fitness Standards Committee (previous positions)
Speakers

• Rama Pidaparti
  • AVP, Global Head, QARA Services, L&T Technology Services, Medical and Life Sciences
  • Over 25 years of Industry experience
  • Software quality and regulatory compliance
  • IT Solutions that support business processes for Life Sciences
  • HIPAA compliance, IT compliance, Infrastructure Qualification, Computerized Systems Validation (CSV), QSR compliance, SOx, ITIL and Information risk management
  • Clinical Trials
  • TPLC of medical devices
  • Supplier Quality, Manufacturing and Post-market
  • Gap analysis and remediation for warning letters, to comply with regulations and standards
  • FDA Case for Quality & CMMI’s maturity model for the Medical Device Industry
  • Process harmonization, postmarket surveillance
  • Global regulatory requirements traceability to compliance evidence.
Speakers

• Bernhard Kappe
  • Pathfinder Development – CEO
  • Chicago Lean Startup Challenge – Executive Director
  • Orthogonal – Founder & CEO
  • Author – *Agile in an FDA Regulated Environment, and Best Practices for Software as a Medical Device and Connected Device Development*
Speakers

• Barbara Fant
  • BSI – Ophthalmic technical reviewer
  • VEO Research Consortium – Founder
  • Clinical Research Consultants – President & Principal Regulatory Consultant
  • Successfully filed > 100 IDE’s, pre-IDE’s, 510(k)’s, and PMA’s
  • ANSI – Subcommittee on ophthalmic standards
Speakers

• Hylton Kalvaria
  • Verana Health – Vice President of Strategic Partnerships
    • Leading Verana’s major partnership initiatives with medical associations, life science companies, and regulatory bodies
  • Flatiron Health – Head, West Coast Life Sciences
    • Founded, built and led the West Coast business, design and execution of Flatiron’s first regulatory-grade projects
  • Genetech – Director, BioOncology Data & Technology Strategy
    • Focused on identifying emerging sources of real world data and utilizing those data across the organization
Things to Keep in Mind

• Software *not regulated* by FDA
  • FFD&CA 520(o) (21 USC 360j(o)) – Administrative support, healthy lifestyle only, EHR functionality, storage, display

• 11 FDA Software-related Guidances
  • [https://www.fda.gov/RegulatoryInformation/Guidances/default.htm](https://www.fda.gov/RegulatoryInformation/Guidances/default.htm)
“In” versus “As”

• Software in a Medical Device (SiMD)
  • An integral part of the function of a hardware medical device
    • Usually embedded, but may be an accessory: 21 CFR 820.30, Design Controls
    • Example: Implantable pacemaker or wearable infusion pump firmware

• 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
    • May be connected to a hardware device but not needed by that device to achieve its intended purpose
    • Example: A computer program that ingests mammography images and outputs an the likelihood of breast cancer
Artificial Intelligence (AI)
Programming computers to perform tasks to mimic human capabilities (e.g., understanding language, recognizing objects and sounds, learning, and problem solving) by using logic, decision trees, machine learning, or Deep Learning

Machine Learning (ML)
Subset of AI that gives “Computers the ability to learn without being explicitly programmed” (Arthur Samuel 1959)

Supervised Learning
(labeled data)

Unsupervised Learning

Deep Learning
Subset of ML - computer teaches itself by exposure to vast amounts of data

Reinforcement Learning

Artificial Intelligence and Machine Learning

AI/ML may be used in a SaMD to develop, train, or perform a software algorithm for a medical intended use
DIGITAL HEALTH AT FDA: AN UPDATE
Thursday, May 2, 2019
Matthew Diamond, MD, PhD
DIGITAL HEALTH AT FDA: AN UPDATE

- Background
- Discussion Paper on AI/ML-based SaMD
- Update on Pre-Cert
IMDRF Global Convergence in Characterizing SaMD

2013 – Foundational vocabulary

2014 – Risk framework based on impact to patients

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

2017 – SaMD Clinical Evaluation ➔ Generating evidence for clinically meaningful SaMD

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.
## IMDRF SaMD Risk Categorization

<table>
<thead>
<tr>
<th>State of Healthcare Situation or Condition</th>
<th>Significance of Information Provided by SaMD to Healthcare Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat or Diagnose</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>II</td>
</tr>
</tbody>
</table>

### Increasing Significance

<table>
<thead>
<tr>
<th>Criticality</th>
<th>IV</th>
<th>III</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

### Increasing Impact/Risk

- Category I
- Category II
- Category III
- Category IV

Arrows illustrate possible change to SaMD definition statement.
Pathway for Continuous Learning
Leveraging Real World Performance Data

SaMD manufacturers are encouraged to leverage SaMD’s technology capability to capture real world performance data to understand user interactions with the SaMD, and conduct ongoing monitoring of analytical and technical performance to support future intended uses.

1. Additional clinical data is gathered.
2. The data may create and support new intended use(s).
3. The SaMD manufacturer will update the clinical evaluation and generate a new definition statement.
4. Then the cycle repeats.
Goals for a Tailored Regulatory Framework

- Enhance patients access to high quality digital medical products
- Enable manufacturers to rapidly improve software products with minor changes
- Maintain a reasonable assurance of safety and effectiveness
- Minimally burdensome, including avoiding unnecessary premarket submissions
“Today, we’re announcing steps to consider a new regulatory framework specifically tailored to promote the development of safe and effective medical devices that use advanced artificial intelligence algorithms.”

Dr. Scott Gottlieb, FDA Commissioner
April 2, 2019
Potential Intersections of AI and FDA

- AI used to develop/study FDA-regulated products
- AI used to oversee FDA-regulated products
- AI in FDA-regulated products
Examples of AI/ML-Based SaMD

FDA News Release

FDA permits marketing of clinical decision support software for alerting providers of a potential stroke in patients

*February 13, 2018*

FDA News Release

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

*April 11, 2018*
AI/ML-Based Medical Devices

Potential to fundamentally transform the delivery of health care:

*E.g., Earlier disease detection, more accurate diagnosis, new insights into human physiology, personalized diagnostics and therapeutics*

Ability for AI/ML to learn from the wealth of real-world data and improve its performance

Already seen AI/ML lead to the development of novel medical devices
AI/ML-Based Medical Devices: Challenges

- Need for large, high-quality, well-curated data sets
- Explain-ability of these “black box” approaches
- Identifying and removing bias
- Providing oversight to an AI-based product that is changing

QuantX
# Clinical Evaluation & Evidence Gathering

## Clinical Evaluation

<table>
<thead>
<tr>
<th>1</th>
<th>Valid Clinical Association</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Generate evidence</strong> to demonstrate a valid clinical association between a SaMD output and a SaMD’s targeted clinical condition</td>
</tr>
</tbody>
</table>

- **Use existing evidence** (e.g., literature searches, original clinical research, professional society guidelines), or
- **Generate new evidence** (e.g., secondary data analysis, perform clinical trials)

<table>
<thead>
<tr>
<th>2</th>
<th>Analytical Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Generate evidence</strong> to demonstrate that the SaMD correctly processes input data to generate accurate, reliable, and precise output data</td>
</tr>
</tbody>
</table>

- Generate evidence as part of quality management system or good software engineering practices

<table>
<thead>
<tr>
<th>3</th>
<th>Clinical Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Generate evidence</strong> to demonstrate that the SaMD’s accurate, reliable, and precise output data achieves its intended purpose in its target population in the context of clinical care</td>
</tr>
</tbody>
</table>

- Generate evidence that shows:
  - The SaMD has been tested for its target population and for its intended use;
  - Users can achieve clinically meaningful outcomes through predictable and reliable use.
Spectrum of ML/AI-Based Algorithms

Locked Algorithm, Discrete Updates

SPECTRUM OF ML/AI-BASED ALGORITHMS

Updates less frequent and performed by human

Updates more frequent and performed by computer

Continuously Adaptive Algorithm
SPS & ACP: A Pre-Determined Change Control Plan

SaMD Pre-Specifications (SPS):
• Delineates the proposed types of modifications to the SaMD (i.e., what types of changes the sponsor plans to achieve)
• Draws a virtual “region of potential changes” around the initial specifications and labeling of the original device

Algorithm Change Protocol (ACP):
• Describes the methods for performing and validating the changes pre-specified in SPS (i.e. how the sponsor intends to achieve the changes)
• Typically specific to the device and type of change
• Expected to contain a step-by-step delineation of the procedures to be followed
SPS & ACP: A Pre-Determined Change Control Plan

SaMD Pre-Specifications (SPS):
- Delineates the proposed types of modifications to the SaMD (i.e., what types of changes the sponsor plans to achieve)
- Draws a virtual “region of potential changes” around the initial specifications and labeling of the original device

Algorithm Change Protocol (ACP):
- Describes the methods for performing and validating the changes pre-specified in SPS (i.e. how the sponsor intends to achieve the changes)
- Typically specific to the device and type of change
- Expected to contain a step-by-step delineation of the procedures to be followed

Good ML Practices (GMLP):
- Accepted practices in ML/AI algorithm design, development, training, and testing that facilitate the quality development and assessment of ML/AI-based algorithms
- Based on concepts from quality systems, software reliability, machine learning, and data analysis, etc
## Algorithm Change Protocol (ACP)

| Data Management | For new training & test data:  
|                 | • Collection protocols  
|                 | • Quality assurance  
|                 | • Reference standard determination  
|                 | Auditing and sequestration of training and test sets  |
| Re-training     | Re-training objectives  
|                 | Changes related to:  
|                 | • ML methods, including architecture and parameters  
|                 | • Data pre-processing  
|                 | Criteria to initiate performance evaluation  |
| Performance Evaluation | Assessment metrics  
|                     | Statistical analysis plans  
|                     | Frequency and triggers for evaluation  
|                     | Performance targets  
|                     | Methods for testing with “clinicians in the loop” when necessary  |
| Update Procedures | Software verification and validation  
|                     | When and how updates will be implemented  
|                     | Plans for global and local updates  
|                     | Communication and transparency to users  |
Typical AI/ML Model Lifecycle

Data selection and management → Model training and tuning → Model validation

- Performance evaluation
- Clinical evaluation

New (Live) Data → Deployed Model

Model monitoring
- Log and track
- Evaluate performance

Legend
- AI Model Development
- AI Production Model
- AI Device Modifications
FDA’s Proposed TPLC Approach Overlaid on AI/ML Workflow

**Good Machine Learning Practices**

- Data selection and management
- Model training and tuning
- Model validation
  - Performance evaluation
  - Clinical evaluation
- Model monitoring
  - Log and track
  - Evaluate performance
- Data for re-training

**Legend**

- AI Model Development
- AI Production Model
- AI Device Modifications
- Proposed TPLC Approach

**Spectrum of ML/AI-Based Algorithms**

- Locked Algorithm, Discrete Updates

- Updates **less frequent** and performed by human

- Updates **more frequent** and performed by computer

**Premarket Assurance of Safety and Effectiveness**

- Review of SaMD Pre-Specifications and Algorithm Change Protocol

**Real-World Performance Monitoring**

- Performance evaluation
- Clinical evaluation

- Data for re-training

**Culture of Quality and Organizational Excellence**

- New (Live) Data
- Deployed Model
- Model monitoring

1. Data for re-training
2. Premarket Assurance of Safety and Effectiveness
3. Review of SaMD Pre-Specifications and Algorithm Change Protocol
4. Real-World Performance Monitoring

www.fda.gov/digitalhealth
FDA Pre-Cert Program

An organization-based streamlined regulatory approach for

Software as a Medical Device (SaMD)

that relies on a demonstrated

Culture of Quality and Organizational Excellence
Five Excellence Principles Proposed

- **Patient Safety**: Demonstration of a commitment to providing a safe patient experience, and to emphasizing patient safety as a critical factor in all decision-making processes.

- **Product Quality**: Demonstration of a commitment to the development, testing, and maintenance necessary to deliver SaMD products at the highest level of quality.

- **Clinical Responsibility**: Demonstration of a commitment to responsibly conduct clinical evaluation and to ensure that patient-centric issues including labeling and human factors are appropriately addressed.

- **Cybersecurity Responsibility**: Demonstration of a commitment to protect cybersecurity, and to proactively address cybersecurity issues through active engagement with stakeholders and peers.

- **Proactive Culture**: Demonstration of a commitment to a proactive approach to surveillance, assessment of user needs, and continuous learning.
FDA’s Software Precertification Pilot Program

- **Building** a working model with continuous public input.
- **Working** with nine participating companies (large and small).
- **Testing** v1.0 throughout 2019 to ensure the same level of **safety and effectiveness** of products as compared to our traditional approach.
Developing the Program with Stakeholder Input

The FDA continues to seek input on the Pre-Cert working model from the public through the public docket. Your input will help shape the next steps that we take to build the Pre-Cert program.
Further Questions or Feedback

www.fda.gov/digitalhealth

DigitalHealth@fda.hhs.gov

Matthew Diamond, MD, PhD
Medical Officer, Digital Health
Center for Devices and Radiologic Health
Office of Strategic Partnerships & Technology Innovation (OST)
Division of Digital Health
U.S. Food and Drug Administration
matthew.diamond@fda.hhs.gov
(301) 796-5386
Comprehensive Compliance Framework for AI-ML-SaMD
Agenda

1. Introduction
2. Challenges
3. Factors of integrated compliance framework
4. Few Examples
5. Relevant references
Introduction – a New World

New Paradigm:
• Using devices collect data and provide/sell useful services to patients in real-time, using/involving patient data. That also involves AI/ML based SaMD (e.g.: patient monitors, actions to take care of Golden Hour), others)

Things to consider:
• This can be bidirectional. We think about AI/ML SaMD mainly as something that changes while it is in use by the patient, improving its safety and effectiveness. But how about when it harvests data and sends it back to the firm? For what uses? How is that handled? What is allowed?
• Collecting this kind of data from users and patients is not typical for medical devices, although there are specific situations (registration, studies, etc, and the new RWD/RWE initiative)

Use environment (important for risk assessment and other issues):
• Hospitals
• Home
• Veterans (DoD)

Don’t forget reimbursement
• Who pays for it and how
Factors – Integrated Compliance Framework

- Change Control is the biggest challenge
- Need Product, IT and other best practices to be part of QMS (for GMLP), covering different use environment scenarios, for internal and external stakeholders
- Define RACI as there are many players coming together in this eco-system
  - Manufacturer with all the suppliers
  - IT / Data hosts (Cloud Operators or Data Center Hosts)
  - Use environments
  - Platform providers (e.g.: Apple, Android, Windows, other)
  - Deployment – App-Stores
  - Regulators (review/approval when applicable) for changes
  - Release Management for changes (after regulator approval, when applicable)
- Examples of different use environments:
  - Hospitals – not too eager to allow wireless connection
  - Veterans – connecting to DoD network needs to comply with Risk Management Framework (used to be DIACAP)
  - Home
  - ITAR potential for dual-use potential items?
  - Security risks - Pacemaker or Insulin Pumps (can be lethal) – Privacy does not affect safety
# Factors to consider when Product has IT (AI/ML/SaMD) - TPLC

<table>
<thead>
<tr>
<th>NPI CONSIDERATIONS</th>
<th>IT CONSIDERATIONS (Traditional)</th>
<th>OTHER OPERATIONAL CONSIDRATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Controls (820.30 + IEC 62304 + TIR 45)</td>
<td>Qualified Infrastructure</td>
<td>Cloud Provider to assure aspects of this +</td>
</tr>
<tr>
<td>Risk Assessment, DHF, DMR, Labeling</td>
<td>Validated Applications</td>
<td>Normal inhouse and post market QSR activities under continuous bidirectional data flow (may or may not involve the MD)</td>
</tr>
<tr>
<td>Regulatory Submissions, reviews, updates</td>
<td>IT best practices for GxP, SOx and HIPAA impacted IT systems (ITIL, ISO 27001, other required controls)</td>
<td>Cyber Security, Privacy and Security (HIPPA &amp; GDPR), Information Risk Management (encryption and penetration testing) and Monitoring</td>
</tr>
<tr>
<td>Changes, reviews, updates, reclassification? (DevOps?)</td>
<td>Use environment centric (home, hospital, Veterans/DoD locations)</td>
<td>RMF (used to be DIACAP), ITAR (dual use)</td>
</tr>
</tbody>
</table>

Very cross-functional involving manufacturer, Platform, COTS, Cloud providers, Regulators for Change Management
Few Examples and IMDRF Risk Category

- Patient Monitors – Used in Hospitals, Veterans Hospitals
- Continuous Glucose Monitoring with Insulin Pumps
- Cancer Detection from scans
- Data used for computing cardiac risk
- Other scenarios: MDIC - NESTcc initiative with RWD/RWE.

<table>
<thead>
<tr>
<th>State of Healthcare situation or condition</th>
<th>Significance of information provided by SaMD to healthcare decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat or diagnose</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-serious</td>
<td>II</td>
</tr>
</tbody>
</table>

SaMD Category
PMS Eco-system

- Co2
- ECG
- NIBP
- SPo2

- Wired and wireless Connections

Bedside PMS

PMS design & development & sensor integration

Central Nursing Station

CNS design & development

Enterprise Integration

Network

Electronic Medical Record (EMR)
# Responsibility matrix (RASCI)

## Product Development

<table>
<thead>
<tr>
<th>Activity</th>
<th>Client</th>
<th>LTTS</th>
<th>CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generate High level Concepts / solutions, System Architecture - Hardware and Software, Indication for use</td>
<td>C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Perform Risk assessment</td>
<td>C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Evaluate Platform, Cloud choices for the solution</td>
<td>C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Finalize Concept / Solution / System Architecture for intended use</td>
<td>A</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Perform IP Search - Prior art search</td>
<td>C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Pre-cert check with Regulator</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Build POC</td>
<td>C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Test POC</td>
<td></td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Technical Review on POC</td>
<td>A</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Update design</td>
<td>C</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Design Transfer</td>
<td>R/A</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Update Risk assessment</td>
<td>C</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Update Design; approval for Proto build</td>
<td>A</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>All kinds of testing</td>
<td>R/A</td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Necessary updates</td>
<td>R/A</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Create DMR</td>
<td>R/A</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Product certification with Regulator</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Responsibility matrix (RASCI)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Client</th>
<th>LTTS</th>
<th>CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess change – Performance, Inputs or Intended Use</td>
<td>R/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check with Regulator based on type of change</td>
<td>R/A</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>Finalize change decision</td>
<td>R/A</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Perform IP Search - Prior art search</td>
<td>A</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Finalize Regulatory submission change documents if change warrants it.</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implement change following QMS for change management</td>
<td>R</td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Build POC</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other activities leading to change completion.....</td>
<td>R/A</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Create DMR</td>
<td>R/A</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Regulatory submissions if applicable</td>
<td>R/A</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Product certification with Regulator</td>
<td>R/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SaMD Pre-Specifications (SPS): The SPS draws a “region of potential changes” around the initial specifications and labeling of the original device. This is "what" the manufacturer intends the algorithm to become as it learns.

Algorithm Change Protocol (ACP): The ACP is a step-by-step delineation of the data and procedures to be followed so that the modification achieves its goals and the device remains safe and effective after the modification. This is "how" the algorithm will learn and change while remaining safe and effective.
GMLP

AI/ML algorithm development involves learning from data and hence prompts unique considerations that embody GMLP. In this paper, GMLP are those AI/ML best practices (e.g., data management, feature extraction, training, and evaluation) that are akin to good software engineering practices or quality system practices. Examples of GMLP considerations as applied for SaMD include:

- Relevance of available data to the clinical problem and current clinical practice;
- Data acquired in a consistent, clinically relevant and generalizable manner that aligns with the SaMD’s intended use and modification plans;
- Appropriate separation between training, tuning, and test datasets; and
- Appropriate level of transparency (clarity) of the output and the algorithm aimed at users.

Source: FDA’s “Proposed regulatory Framework for Modifications to Artificial Intelligence /Machine Learning (AI/ML) - Based software as Medical Device (SaMD)”
**Relevant Best Practices Standards & References**

- **Best Practices and Standards:**
  - QSR, Design Controls, ISO-13485-2016, IEC 62304, IEC 60601 TIR 45, HL-7, ISO-27001, ITIL V3, SSAE-No. 16, RMF, NIST 800-53

- **References:**
  - IMDRF’s SaMD - Software as a Medical Device (SaMD) – (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM524904.pdf)
  - FDA proposes updated cybersecurity recommendations to help ensure device manufacturers are adequately addressing evolving cybersecurity threats (https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm623624.htm)
  - Proposed regulatory Framework for modification to AI/ML based SaMD (https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/SoftwareasaMedicalDevice/UCM635052.pdf)
  - Risk Management Framework
  - Software as a Medical Device (SaMD): Clinical Evaluation
    (http://www.imdraf.org/docs/imdraf/final/consultations/imdraf-cons-samd-ce.pdf)
  - Software as a Medical Device (SaMD): Application of Quality Management System
Thank you
Rama K Pidaparti
ORTHOGONAL

AI in SaMD

Opportunities and Challenges in Consumer Facing Solutions
Orthogonal Focus

Software as a Medical Device

Connected Devices

Patient and Clinician Engagement
AI in Radiology/Imaging

• Largest Number of Cleared AI SaMD
• Data Quality: Inputs from Cleared Devices Operated by Trained Staff
• Data Quantity: Availability of Large Data Sets
• Interpretation and Annotation of Images by Specialist Clinicians
• Tied to Patient Record in EMR
• Continuous Learning is Feasible

• Challenges: Interaction with/Adoption in Clinical Practice
AI in Consumer Facing SaMD

• Leveraging Implanted/Wearable/Portable Devices, Wireless Communication, Consumer Supplied Smartphones and Cloud Services
• Data Sources: Device, Smartphone Sensors, Patient Input, Third Party Datasets
• Used by Consumers “In the Wild”
AI in Consumer Facing SaMD

- Home Based Screening/Diagnostics
- Continuous Monitoring and Risk Stratification/Prediction
- Managing treatment, digital therapeutics
- Modulating/Changing Therapy – Therapy Adjustment
AI-based Personalized Anomaly Detection for At-Risk Patients
SmartSignal

- Sensors on Aircraft Engines
- Establish Baseline
- Predict Engine Failure Based on Differentials to Baseline
- Extend to Other Devices – “Device Agnostic”
- Sold to GE Intelligent Platforms/GE Digital in 2011
- Monitors more than 16,000 Assets worth $37 Billion across industries and around the world.
VGBio/PhysIQ

Can we apply this to the Human Heart?
• Establish Baseline
• Predict Heart Attacks Based on Differentials to Baseline?
• Testing Algorithm on Historical Data Sets
• Proprietary Bluetooth Enabled Vital Signs Wearable
• Android Mobile Application
• Analytics in the Cloud
• Collaboration/Trial with the Veterans Administration
PhysIQ

- First Clearance: 2015, 510(k) – Personalized Physiology Engine (PPA Engine)
  Product Classification: Multivariate Vital Signs Index.
- Switch to using off the shelf, FDA cleared continuous monitors, then a platform that can integrate multiple clinical grade wearables.
- Switch to Deep Nets for Offline Learning – Faster and Better
- 2018 Trial Results – Multivariate physiological telemetry from disposable wearable sensors provided accurate early detection of impending rehospitalization with a predictive accuracy comparable to implanted devices.
- 2018 Clearance for Afib Algorithm
- Currently being used by leading payers and providers to better care for patients recently discharged from the hospital, recovering at a skilled nursing facility or enrolled in a home health program, as well as for clinical trials.
Challenges of AI in Consumer Facing SaMD

• Quality and Quantity of Data Sources.

• Reference Standards and Ground Truth:
  – May be difficult/costly to obtain (e.g. validated questionnaire vs. lab test on blood sample.)
  – May be apples to oranges (e.g. ambulatory vs. lab/clinical setting vs physician scoring.)

• What do patients and clinicians see, when?
Lessons Learned in Consumer Facing AI

• Planning for Input Data Quality and Change
• What are early warning signs?
• Planning for Updates - Most Often: Offline Learning and Locked Algorithms
• Use real world data to move up the evidence (and claims) curve
• Understand Your Users
Clinical Evaluation of SaMDs: Regulatory and Clinical Challenges

Barbara Fant, Pharm.D.
Clinical Research Consultants, Inc.

3308 Jefferson Avenue, Upper Level
Cincinnati, Ohio 45220
513.961.8200
BSFant@CRC-Regulatory.com
Software as a Medical Device (SAMD): Clinical Evaluation

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 8, 2017.
The draft of this document was issued on October 14, 2016.
Final Document

Title: Software as a Medical Device (SaMD): Clinical Evaluation

Authoring Group: Software as a Medical Device Working Group

Date: 22 June 2017
Other IMDRF Documents You Need to Know

- **SaMD N10**: Software as a Medical Device (SaMD): Key Definitions --

- **SaMD N12**: Software as a Medical Device (SaMD): Possible Framework for Risk Categorization and Corresponding Considerations --

- **SaMD N23**: Software as a Medical Device (SaMD): Application of Quality Management System --
Regulatory Challenges

- Regulatory Classification
- Clinical Risk Categorization
  - Intended use can change regulatory class and clinical category
- Guidances are global for multiple regulatory environments
  - U.S. FDA or global strategy
- 510K SaMDs
  - Predicate device
  - De Novo (supportive clinical evidence)
- GCP Issues
- Incorporating QMS
Clinical Evaluation Challenges

- GCP Issues
  - SaMDs typically not designed for clinical trials
    - HIPAA
    - Data integrity
    - Interfacing with other medical devices, SaMD, general purpose software
    - Integrating SaMD data with clinical database
    - Monitoring/data verification

- Standardization across clinical sites
  - Technology environment (cloud, mobile app, server)
  - Operating system/hardware

- Software version (updates, upgrades)
- Cybersecurity
- Installation
SaMD N41 Clinical Evaluation

Clinical Association
between a SaMD output and a Clinical Condition
- Literature searches, Original Clinical Research, Professional Society Guidelines, Secondary Data Analysis, Clinical Trials

Product Performance
Verify & Validate
- Analytical / Technical Validation
  - Accuracy, Reliability, Precision...
- Clinical Validation
  - Sensitivity, Specificity, Odds Ratio...

SaMD Definition Statement
- Intended Medical Purpose of a SaMD
  - Treat or Diagnose
  - Drive Clinical Management
  - Inform Clinical Management
- Targeted Healthcare Situation or Condition of a SaMD
  - Critical
  - Serious
  - Non-Serious

SaMD Categories
- Treat or Diagnose
- Drive Clinical Mgmt
- Inform Clinical Mgmt

<table>
<thead>
<tr>
<th>Category</th>
<th>Treat or Diagnose</th>
<th>Drive Clinical Mgmt</th>
<th>Inform Clinical Mgmt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical</td>
<td>IV</td>
<td>III</td>
<td>II</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

SaMD N23 Quality Management System

SaMD N12 Risk Categorization Framework

SaMD Realization and Use Processes
- Requirements, Design, Develop, Verify & Validate, Deploy, Maintain, Retire

SaMD Lifecycle Support Processes
- Planning, Risk Management, Documentation, Measurement, Outsourcing

Leadership and Organizational Support
- Personnel, Infrastructure, Work Environment
SAFETY NEEDS TO BE ADDRESSED EARLY IN DESIGN AND DEVELOPMENT

IMDRF N12:2014 SaMD Risk Categorization
IMDRF N23:2015 SaMD Application of Quality Management System

Clinical evaluation is a continuous, iterative quality process
SaMD

- Software intended to be used for one or more medical purposes without being part of a hardware medical device
- Can interface with other devices
SpecifEye Definition Statement

No Medical Purpose

<table>
<thead>
<tr>
<th>Intended Medical Purpose</th>
<th>SpecifEye ocular biomechanical modeling software is intended for use as a simulation tool to provide a quantitative and qualitative evaluation of the simulated effects of surgical treatments on the structural integrity of the cornea.</th>
</tr>
</thead>
<tbody>
<tr>
<td>≠ Treat or diagnose</td>
<td></td>
</tr>
<tr>
<td>≠ Drive clinical management</td>
<td></td>
</tr>
<tr>
<td>≠ Inform clinical management</td>
<td></td>
</tr>
<tr>
<td>Healthcare situation or condition intended for</td>
<td>SpecifEye is indicated for use in performing mathematically derived pre-treatment modeling on imported corneal geometry data from a previously acquired corneal tomography.</td>
</tr>
<tr>
<td>≠ Critical</td>
<td></td>
</tr>
<tr>
<td>≠ Serious</td>
<td></td>
</tr>
<tr>
<td>≠ Non-serious</td>
<td></td>
</tr>
<tr>
<td>Describe core functionality</td>
<td>SpecifEye calculates strains and stresses from the modeling to produce simulated outcomes for corneal curvature, corneal pachymetry, corneal aberrations and other outputs as indicators of biomechanical changes that affect corneal structural integrity following ocular surgery.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## SpecifEye Definition Statement

### Medical Purpose

<table>
<thead>
<tr>
<th>Intended Medical Purpose</th>
<th>SpecifEye ocular biomechanical modeling software is intended for use as a simulation tool to aid in the treatment of keratoconus.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat or diagnose</td>
<td></td>
</tr>
<tr>
<td>Drive clinical management</td>
<td>SpecifEye is indicated for use in performing mathematically derived pre-treatment modeling on imported corneal geometry data from a previously acquired corneal tomography to select treatment parameters for CXL treatment of keratoconus.</td>
</tr>
<tr>
<td>Inform clinical management</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Healthcare situation or condition intended for</th>
<th>SpecifEye calculates strains and stresses from the modeling to produce simulated outcomes for corneal curvature, corneal pachymetry, corneal aberrations and other outputs as indicators of biomechanical changes that affect corneal structural integrity following ocular surgery for monitoring the progression of keratoconus.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Critical</td>
<td></td>
</tr>
<tr>
<td>• Serious</td>
<td></td>
</tr>
<tr>
<td>• Non-serious</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Describe core functionality</th>
<th></th>
</tr>
</thead>
</table>
**Definition Statement Impacts Risk Categorization**

- Risk mitigation is proportional to risk and impact
  - Significance of information provided by SaMD to health decision
  - State of healthcare situation or condition
  - Higher the risk, greater the need for independent oversight

<table>
<thead>
<tr>
<th>State of Healthcare Situation or Condition</th>
<th>Significance of Information Provided by SaMD to Healthcare Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TREAT OR DIAGNOSE</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>II</td>
</tr>
</tbody>
</table>

**Lower Risk/Impact**
<table>
<thead>
<tr>
<th>State of Health Care Situation or Condition</th>
<th>Critical</th>
<th>Serious</th>
<th>Non-Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease or Condition</td>
<td>Life-threatening</td>
<td>Moderate progression</td>
<td>Slow, predictable progression</td>
</tr>
<tr>
<td>Curable</td>
<td>No</td>
<td>Often</td>
<td>Yes or No; can manage effectively</td>
</tr>
<tr>
<td>Therapeutic Intervention</td>
<td>Requires major</td>
<td>Requires not major</td>
<td>Requires minor</td>
</tr>
<tr>
<td>Invasive</td>
<td>Generally Yes</td>
<td>Yes or No</td>
<td>Generally No</td>
</tr>
<tr>
<td>Time critical</td>
<td>May be critical</td>
<td>Generally no</td>
<td>No</td>
</tr>
<tr>
<td>SaMD Output Error Detection</td>
<td>No time to detect if time sensitive</td>
<td>Time to detect</td>
<td>Time to detect</td>
</tr>
<tr>
<td>Target Population</td>
<td>Fragile</td>
<td>Not fragile</td>
<td>Individual – may or may not be patients</td>
</tr>
<tr>
<td>Users</td>
<td>Specialized trained users</td>
<td>Specialized trained users or lay users</td>
<td>Specialized trained users or lay users</td>
</tr>
</tbody>
</table>
Multiple Types of Risk

- **Disease or condition**
  - Type, severity, progression

- **Usability of the SaMD**
  - User type (e.g. trained physician)
  - Level of reliance on SaMD output
  - Transparency of inputs/outputs

- **SaMD output**
  - Can erroneous output be detected by user
  - Level of influence on clinical intervention
  - Known specificity of output
  - Confidence in the output (clinical maturity)
  - Comparison with standard of care methods
SpecifEye Risk Categorization

- Output informs clinical management
- Keratoconus
  - Progression generally slow; rapid in pediatrics
  - Not curable, can be managed
  - Treatment may or may not be invasive
  - Adults and pediatrics
- Output not time critical for diagnosis or intervention
- Specialized trained users

### State of Healthcare Situation or Condition

<table>
<thead>
<tr>
<th>State of Healthcare Situation or Condition</th>
<th>Significance of Information Provided by SaMD to Healthcare Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TREAT OR DIAGNOSE</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>II</td>
</tr>
</tbody>
</table>

### Higher Risk/Impact

- Critical
- Serious
- Non-Serious
Set of ongoing activities conducted to perform an assessment and analysis of SaMD’s clinical safety, effectiveness and performance as intended in SaMD definition statement
Valid clinical association between SaMD output and targeted clinical condition

SaMD provides the expected technical and clinical data
- Analytical validation
  - Accuracy, reliability, precision
- Clinical validation
  - Sensitivity, specificity, odds ratio
Analytical & Clinical Validation

**Microstructure-based material model**

- Isotropic matrix with depth-dependent properties
- Collagen fibrils with crimp and angular density functions
- Baseline material constants from iFE of experimental inflation data

Pinsky et al., 2005
Freed & Doehring, 2005
Aghamohammazadeh et al., 2004

- Published modeling methodology
- Published predictive accuracy
- Validated using clinical dataset to establish model
- Validated model correlates with clinical outcomes for each condition
Clinical Evaluation Special Considerations

- Device interactions
- Link input data with output database
- User input error
- Cybersecurity
- Normative database continuously learning
- Training
- Installation, cloud access
- Data transfers and archives
- Leverage real world data??

- Linking study data to output data.
- HIPAA
- Data Issues
Regulatory & Clinical Success

Success requires partnership to put the right team and the right development plan together

- Upfront planning is essential
- Know your SaMD
- Qualified, multidisciplinary project team
- Adequate resources – realistic expectations
- Good clinical design with risk mitigation
  - Reliable input information
  - Reliable output data
  - Apply worst case risk analysis – what can go wrong?
- Good assumptions are critical for study success
- Keep it simple
- Plan for the downside; take the upside
Verana Health: Reinventing Research with Real-World Evidence

Hylton Kalvaria
Vice President, Strategic Partnerships
Our Goal: Reinvent Evidence Generation by Flipping the Paradigm from Prospective to Retrospective

Raw EHR Data +Harmonization +Images +Claims Data +UDI Clinical Trial
The American Academy of Ophthalmology, the American Academy of Neurology, and industry-leading investors came together to form Verana Health.
Today, Verana Health is assembling the largest clinical databases in medicine to accelerate research for patients.
# Verana’s Clinical Databases

## The IRIS® Registry
- Five years of longitudinal EHR data
- 222 million patient visits
- 52 million unique patients
- 13,150 contributing physicians
- 80%+ of AAO membership participating
- 50+ EHRs integrated

## The Axon Registry®
- Five years of longitudinal EHR data
- 5 million patient visits
- 1+ million unique patients
- 2,000+ contributing physicians
- 15%+ of AAN membership participating
- 30+ EHRs integrated
Aggregated Clinical Data Sets Formed at the Nexus of Technology and Regulation

**TECHNOLOGY**
- Widespread adoption of electronic health records
- Advances in interoperability
- Improvements in data processing

**REGULATION**
- HITECH Act of 2009
- MACRA and MIPS quality reporting requirements

Data aggregation at scale in QCDRs
“Because they include data covering the experience of physicians and patients with the actual use of new treatments in practice, and not just in research studies, the collective evaluation of these [real-world] data sources has the potential to inform clinical decision making by patients and providers, develop new hypotheses for further testing of new products to drive continued innovation and inform us about the performance of medical products.”

- Scott Gottlieb, former FDA Commissioner
Verana’s technology platform transforms large clinical data sets into meaningful insights through:

- Data unification across different EHRs and entry formats
- Data curation and validation
- Optimized data analytics infrastructure to accelerate time-to-insight
Analytic Capabilities

Verana’s analytics are powered by:

- Clinical data scientists with domain expertise
- Algorithms team with deep experience applying machine learning techniques to unstructured clinical notes
Real-World Evidence Informs the Entire Lifecycle

- Clinical Trial Operations
- Sales and Marketing
- Medical Affairs
- Outcomes Research
Clinical Journey for Wet AMD (Example)

Patient visits general ophthalmologist for vision distortion. The doctor suspects wet AMD and refers to retina specialist.

Retina specialist diagnoses patient with wet AMD and prepares patient for procedure.

Retina specialist injects patient’s left eye with anti-VEGF therapy. Staff schedules next treatment visit.

Short and long term follow up with retina specialist.

<table>
<thead>
<tr>
<th>VISIT 1</th>
<th>VISIT 2</th>
<th>ONGOING</th>
</tr>
</thead>
</table>

**Data Collected**
- Patient demographics
- Insurance
- Provider sub-sPECIALTY and geography
- Referral information from clinical note
- Visual acuity value
- VA method
- Eye-level data
- Diagnosis
- Procedure (HCPCS/CPT)
- Medication
- Treatment interval
- Treatment pattern
- Long-term outcomes
- Adverse events
Generalized Framework for Any Intervention Type

History → Diagnosis → Intervention → Outcome(s)

- Drug
- ‘Traditional’ Device
- SaMD
Questions for Constructing an RWE Study for SaMD

- How will SaMD-generated data be linked to EHR (clinical) data?
- What is the inclusion / exclusion criteria specific to the intended population?
- What inputs (e.g., clinical data) does the SaMD use or collect?
- What is the therapeutic intent of the SaMD and what are follow-up actions, if any?
- What is the specific output from the SaMD? In what format?
Thank you!

Hylton Kalvaria
hylton@veranahealth.com