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DIGITAL HEALTH DEVICES

SOFTWARE AS A MEDICAL DEVICE (SAMD)

MANUFACTURING, SAFETY, AND FDA APPROVAL

Bhanu Sharma, ND, PhD

Regulatory Compliance Leader

Stanford Center for Clinical Research

Email: sharmab@stanford.edu

Agenda

1. Digital Health, Devices, Systems
2. SAMD Development and Manufacturing
3. Safety & Regulatory Challenges
4. Putting into context
5. Summary & Key Takeaways

1. Digital Health, Medical Devices, Systems

Digital Health- What it is?

"…a wide variety of software and data technologies (e.g., data science, advanced analytics, artificial intelligence, electronic health records (EHRs), virtual and augmented reality), hardware (e.g., smartphones, tablets, computers, health trackers, wearable technologies, sensors, **medical devices**), and services or solutions (e.g., video conferencing, mHealth apps, remote monitoring)"

Services and solutions for Health Management

References:

- ***Sharma, BP.*** **21 CFR Part 11 Perspectives in SaMD and Software Systems, Paper presented at Advarra Onsemble Fall Conference 2021**
- ***Perez, MV et al*****. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation, N Engl J Med 381:1909-1917, 2019**
- ***Turakhia et al.*** **Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study, American Heart Journal 207, 66-75, 2019**

Notes:

- Not all digital health systems are medical devices
- Everchanging boundary
- Regulatory landscape adjustment to current need

Digital Health: Technology & Clinical Areas

Technology Category

- Wearables, Sensors, and Other Devices
- Mobile and Web Applications
- Artificial Intelligence (AI), Machine Learning (ML), and Algorithms
- New Clinical Care Models
- Health IT, Infrastructure, and Data Management

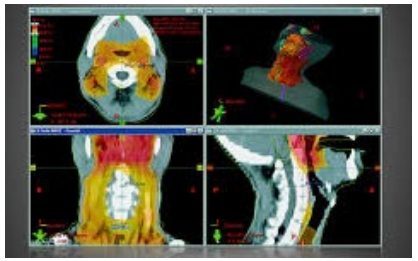
Clinical Areas

- Autoimmune
- Cardio-metabolic
- Critical Care/ ICU
- Dermatology
- Hematology-oncology

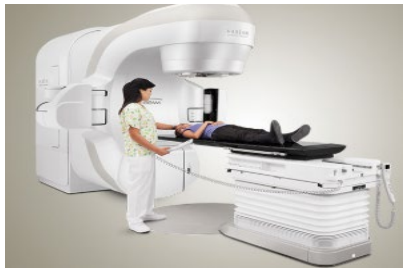
Medical Device: FDA Definition

- **"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,**
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

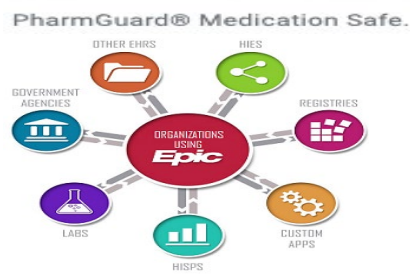
Medical Devices & Systems in Clinical Research



- **Medical Devices**
  - Treatment Planning Software:Eclipse)Connected to device
  - Treatment Systems: TrueBeam
  - Both software and systems are connected

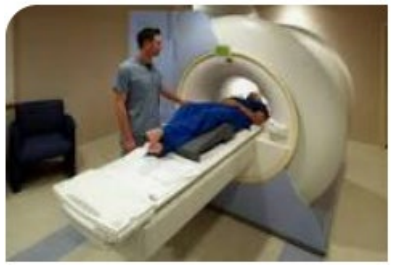


- **Software system- not a medical device**
  - Software to control pumping of medication
  - Electronic Patient Diary (ePRO)
  - EHRS (Electronic Health Record System
  - Excel file, Smartsheet, Database



Software as a Medical Device (SAMD)

- SAMD is a software
- Can perform one or more functions
- May be embedded in a piece of hardware
- Performs the medical function (standalone software)
- Works on general purpose computing platform
- May interface with general-purpose hardware and software
- Examples:
  - Is SAMD: ECG, and IRN Apps on Apple watch
  - Is not SAMD: Software driving the hardware magnet is integral to the function of hardware in MRI



2. SAMD Development & Manufacturing

Regulation, Standards, Guidelines

21 CFR 820 (QSR)- FDA Regulation

- 820.40 Design Controls: Design input/output, review, verification, validation, transfer, change management, Design History File (DHF)
- Process Validation- meets predetermined specification

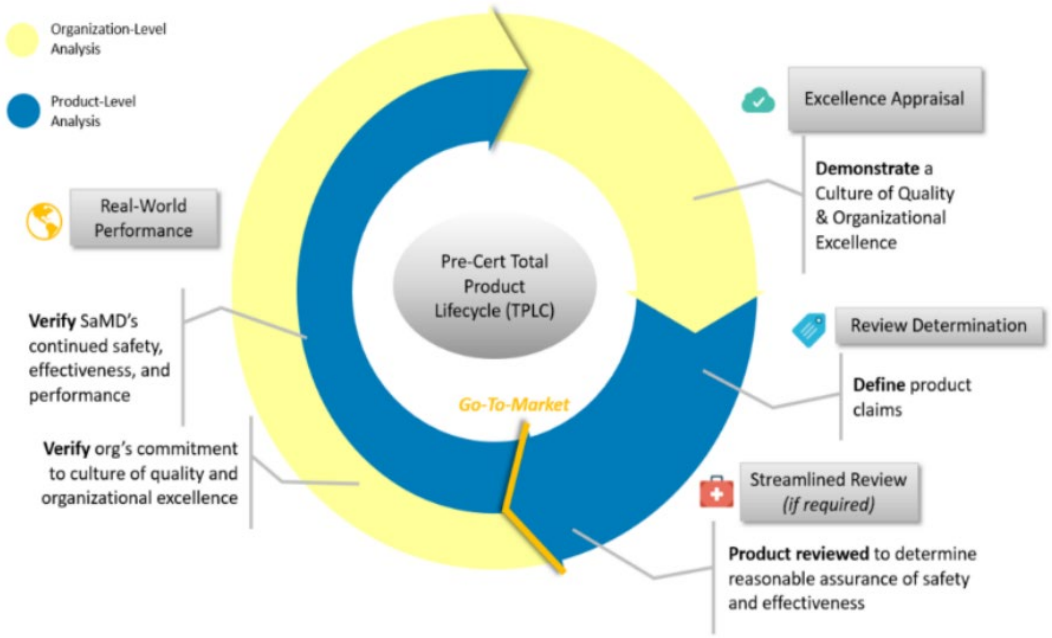
ISO 13485:2016- EU Standard

- Design and development- other same as 21 CFR 820 Design Control
- Design and Development File (same as DHF)

SAMD QMS by IMDRF (International Medical Device Regulator Forum)

Total Product Life Cycle & FDA Pre-registration

TPLC (Apple, Fitbit, J&J, Verily, Roche…)

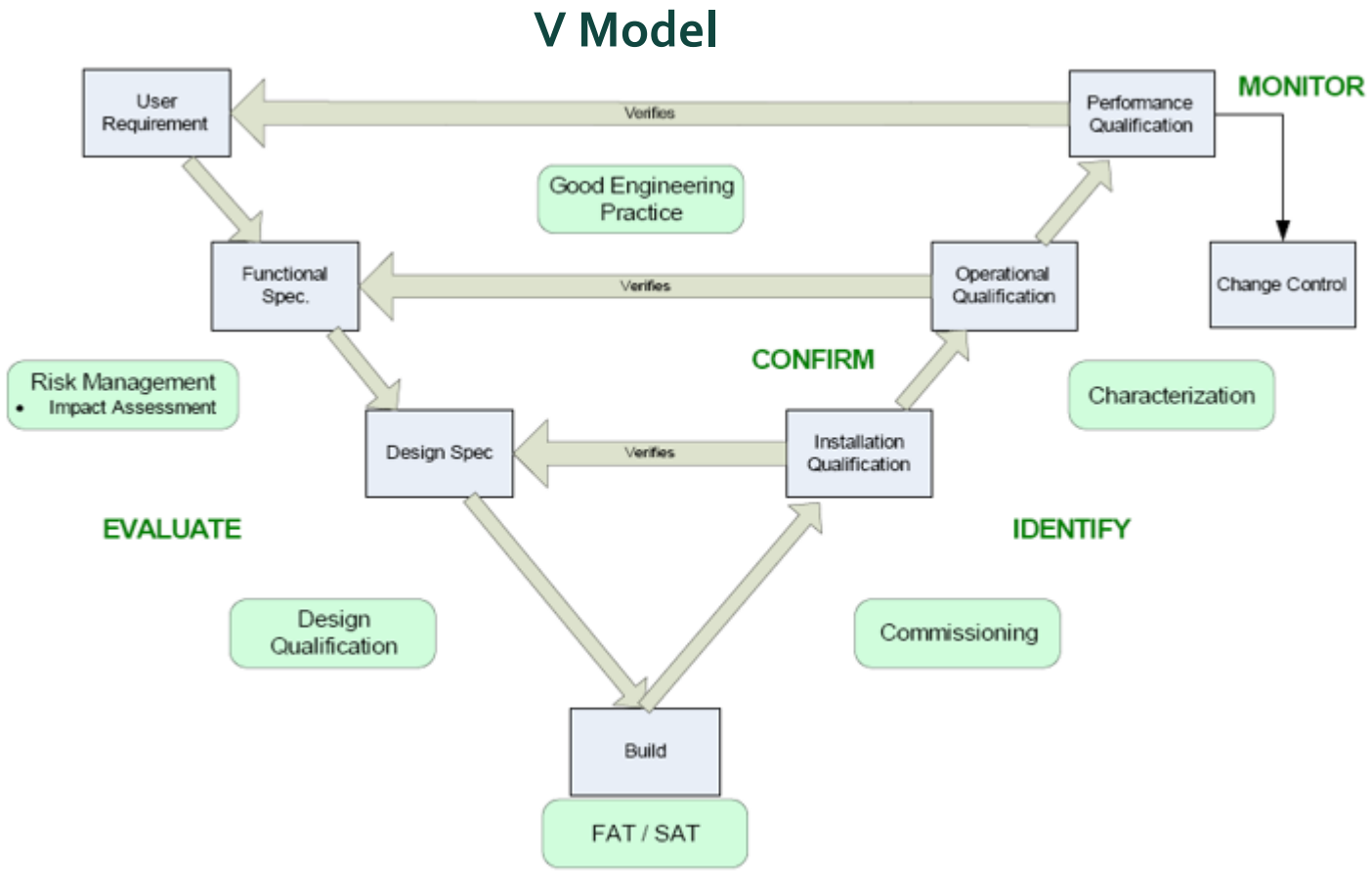


Approval Tips

- Engage FDA early
- Classify SAMD/ Request FDA to classify
- Prove safety and efficacy
- 510(k) or De Novo submission
- Wait and pray!

Design Control and More…

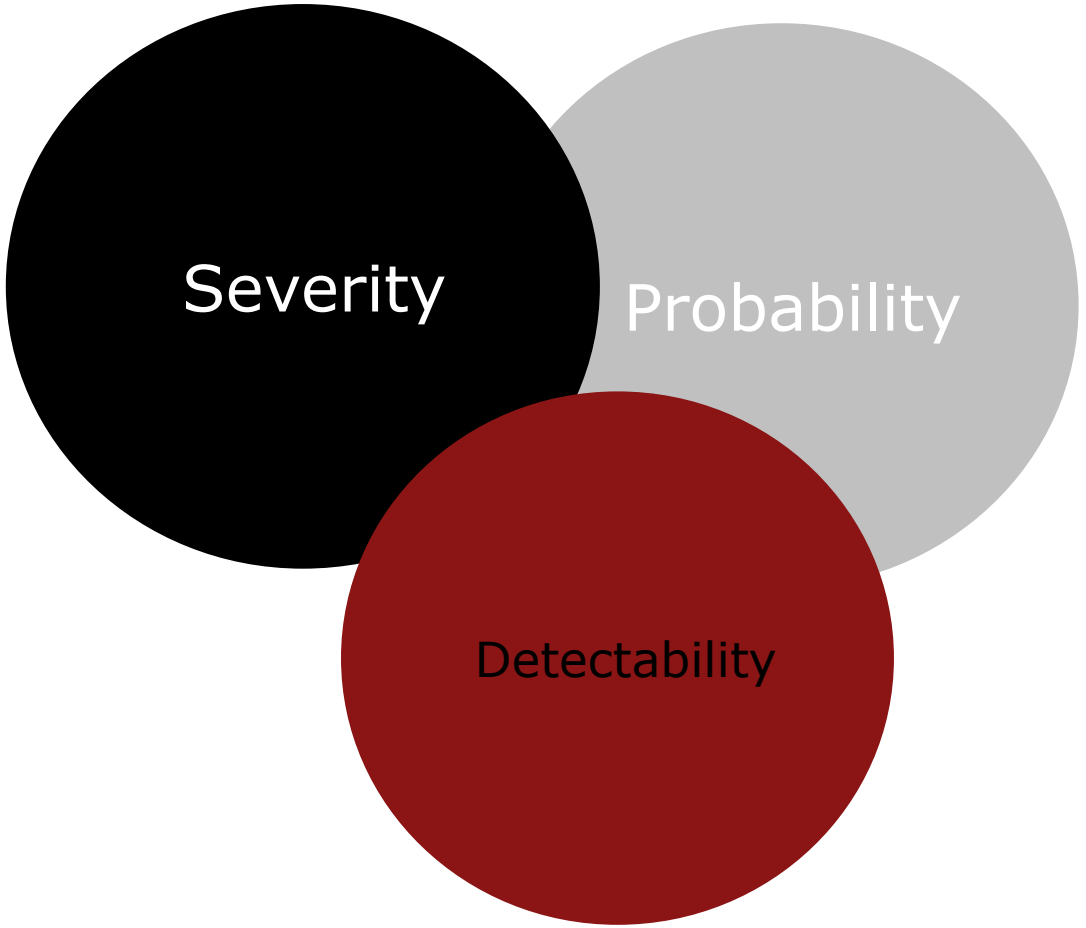
Waterfall Model



3. Safety & Regulatory Challenges

Safety & Risk Management

Failure Mode Effect Analysis (FMEA) Fault Tree Analysis (FTA)

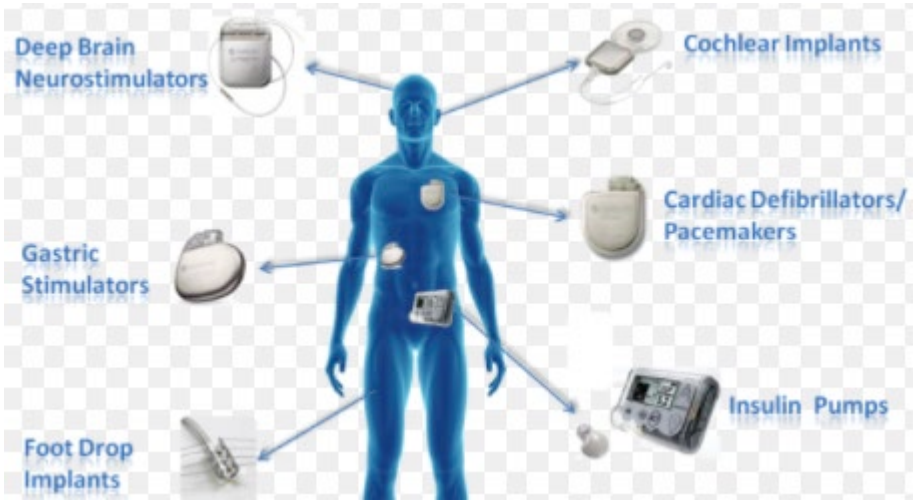


SAMD Main Risks

Risks

- Accessibility
- Cybersecurity
- Interoperability
- Data Integrity
- Data security

Examples

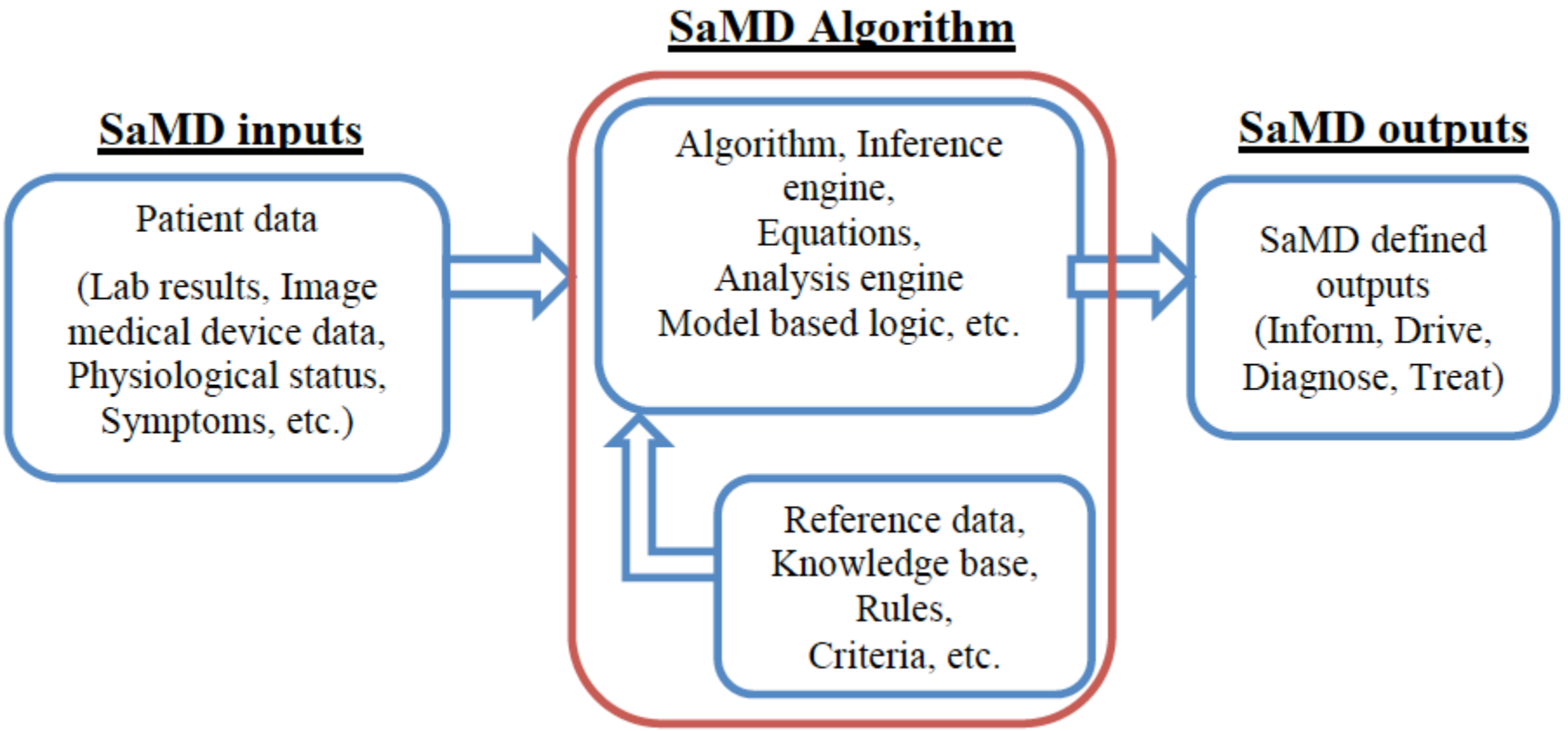


Identified risk to health and mitigation- example ECG SAMD

Risk to Health	Mitigation (Hazard, severity, detectability)
Poor quality ECG signal to detect arrhythmia	Clinical performance testing
Misinterpretation and/or over-reliance on device output	Human factor testing; Labeling
False negative result	Clinical performance testing
False positive	Clinical performance testing, V&V, Hazard analysis, non-clinical testing such as third-party lab testing

4. Putting into Context

SAMD Clinical Evaluation Process- Basic Programming Model



Clinical Evaluation- Validation

① Valid Clinical Association	② Analytical Validation	③ Clinical Validation
Is there a valid clinical association between your SaMD output and your SaMD's targeted clinical condition?	Does your SaMD correctly process input data to generate accurate, reliable, and precise output data?	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 SAMD *output* clinically accepted or well-founded ?

- Output, for example, may be concept, conclusion, measurement

Does the *output* correspond accurately in the real world to the healthcare situation?

- Valid clinical association is an indicator of the level of clinical acceptance and confidence assigned to the clinical significance

Analytical and Technical Validation

Analytical and Technical Validation

- Accuracy
- Repeatability
- Reproducibility (Precision)

Meets specification

Specification conforms to intended and user needs

Clinical Validation

Does it produce meaningful, measurable and patient relevant outcome

- Diagnosis, treatment, prediction of risk, prediction of treatment response
- Positive impact on individual or public health

Clinical validation is performed pre-market and post-market and validates SAMD algorithms

Comparing with an existing approved device or de-novo submission

SAMD categorization framework

State of Healthcare Situation or Condition	Significance of information provided by SaMD to the 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 Examples based on Categorization

Category IV

- SAMD for diagnostic image analysis for making treatment decision of acute stroke
- SAMD data to screen for mutable pathogens, e.g., COVID-19

Category III

- SAMD for radiation treatment planning system
- SAMD providing info by taking pictures and monitoring growth to diagnose skin lesion

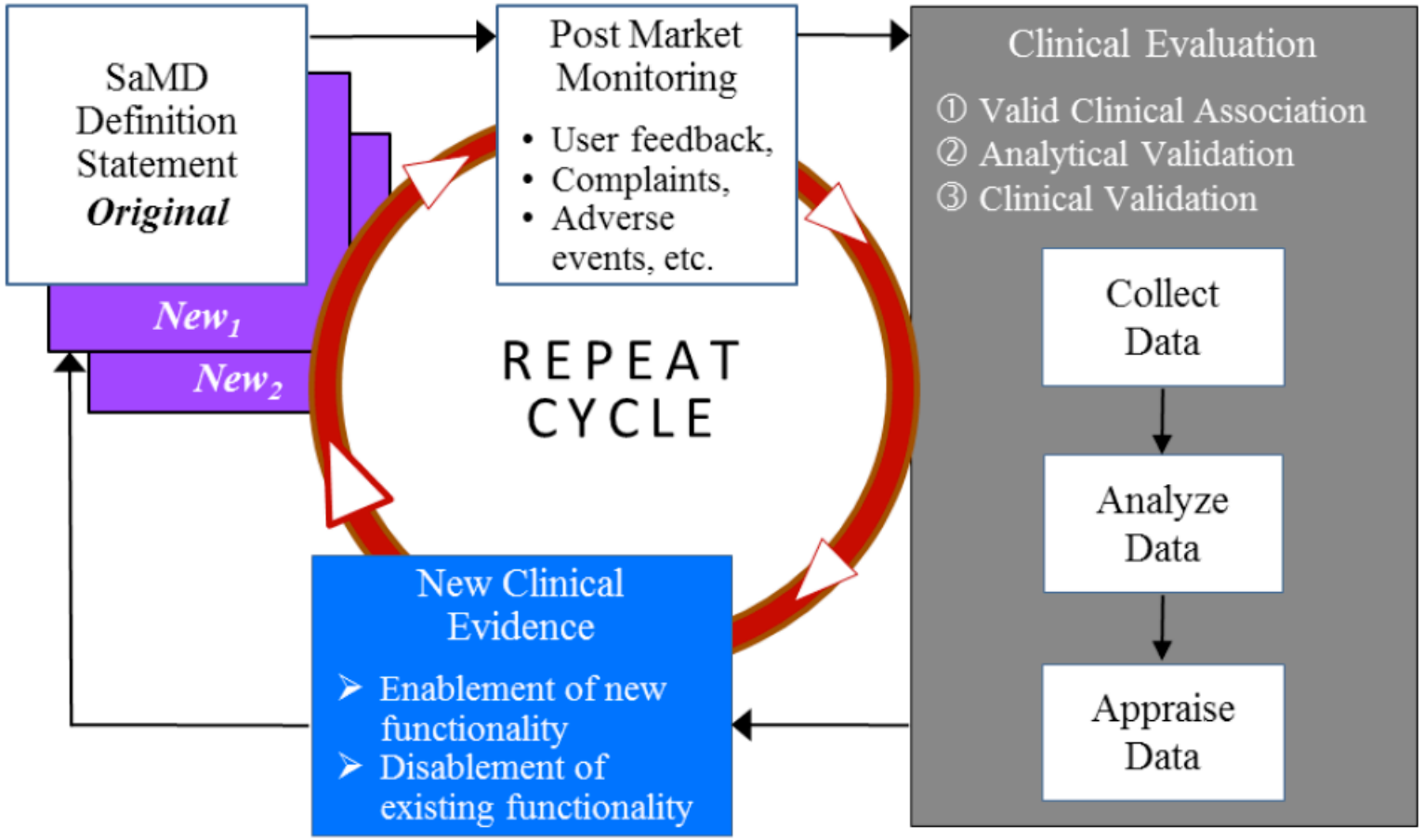
Category II

- SAMD that analyzes heart rate data for a clinician to aid in diagnosis of arrhythmia
- SAMD data for predicting risk score for developing stroke or heart disease

Category I

- SAMD send walking speed, heart rate, blood pressure info
- SAMD image data info that guides next diagnostic action of astigmatism

Real World Performance



3. Summary and Key Takeaway

Summary and Key Takeaway

Digital Health has brought a new paradigm shift. Traditional medical devices (hardware and/or software)

Stand-alone software that is used to diagnose/ treat a disease is called Software as a Medical Device (SAMD)

Implement IMDRF Quality System. Follow robust design control (FDA CFR 820, ISO 13485) and Risk Management (ISO 14971) for deployment

Clinical Evaluation both pre- and post market is a must for SAMD to ensure its safety and performance

Real world performance is a continuous process to improve safety of SAMD and confidence of SAMD acceptance for its use

We are all learning including FDA, NIH, WHO!

Questions/ Comments

email Bhanu Sharma: sharmab@stanford.edu