Regulatory Science in CDRH's Office of Science and Engineering Laboratories

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Division of Biomedical Physics
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health

June 13, 2019

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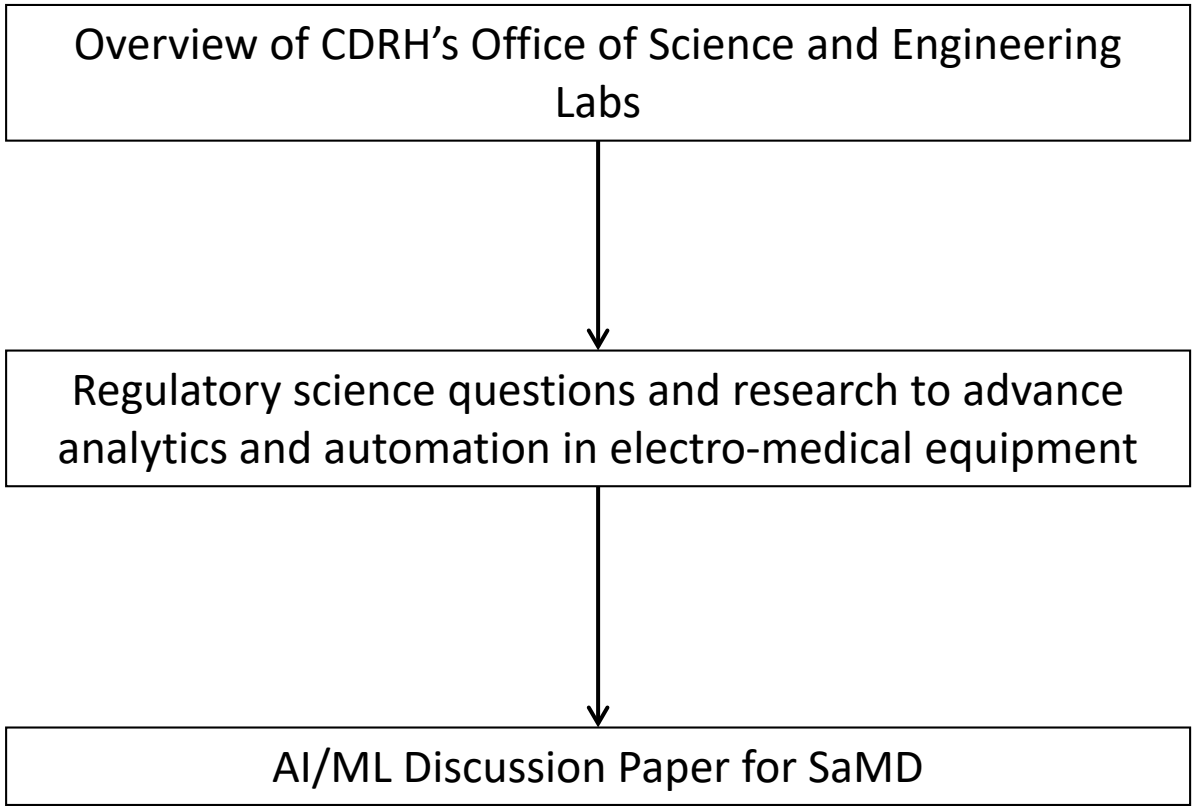
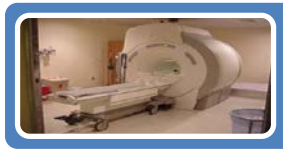

Overview of CDRH's Office of Science and Engineering Labs
Regulatory science questions and research to advance analytics and automation in electro-medical equipment
AI/ML Discussion Paper for SaMD

FDA U.S. FOOD & DRUG ADMINISTRATION

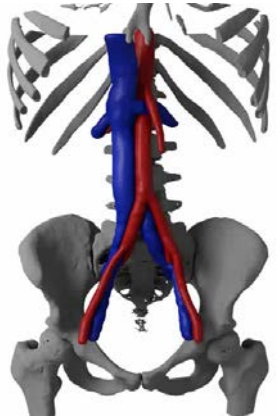
FDA

-  Center for Food Safety & Applied Nutrition
-  Center for Drug Evaluation & Research
-  Center for Biologics Evaluation & Research
- 

Center for Tobacco Products
-  Center for Devices & Radiological Health
-  Center for Veterinary Medicine
-  National Center for Toxicological Research

CDRH Vision

- Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.
- The U.S. is the world's leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety.
- U.S. post-market surveillance quickly identifies poorly performing devices, accurately characterizes real-world performance, and facilitates device approval or clearance.
- Devices are legally marketed in the U.S. and remain safe, effective, and of high-quality.
- Consumers, patients, their caregivers, and providers have access to understandable science-based information about medical devices and use this information to make health care decisions.



CDRH in Perspective

1900
EMPLOYEES

18k
Medical Device Manufacturers

183k
Medical Devices
On the U.S. Market

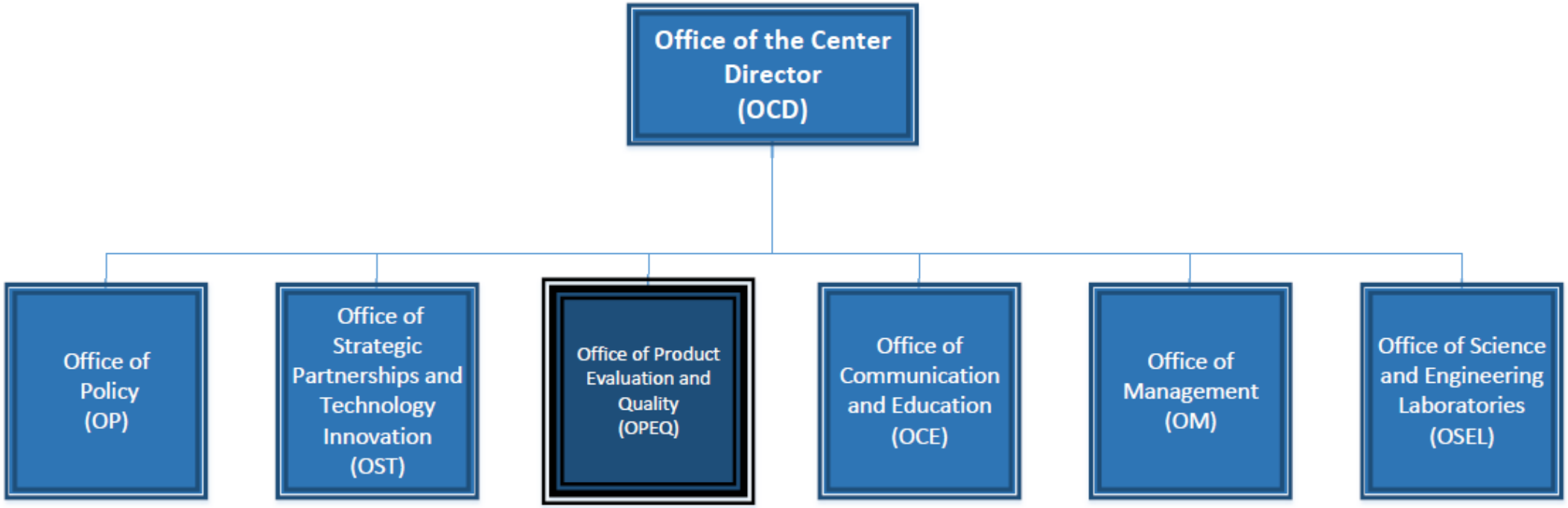
22k/year
Premarket Submissions
includes supplements and amendments

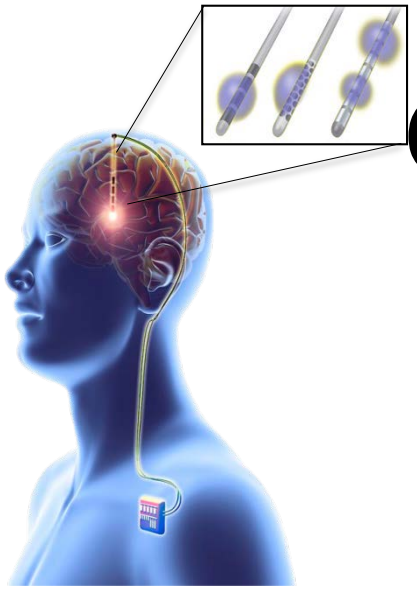
570k
Proprietary Brands

25k
Medical Device Facilities Worldwide

1.4 MILLION/year
Reports on medical device adverse events and malfunctions

CDRH Structure After Reorg Implementation

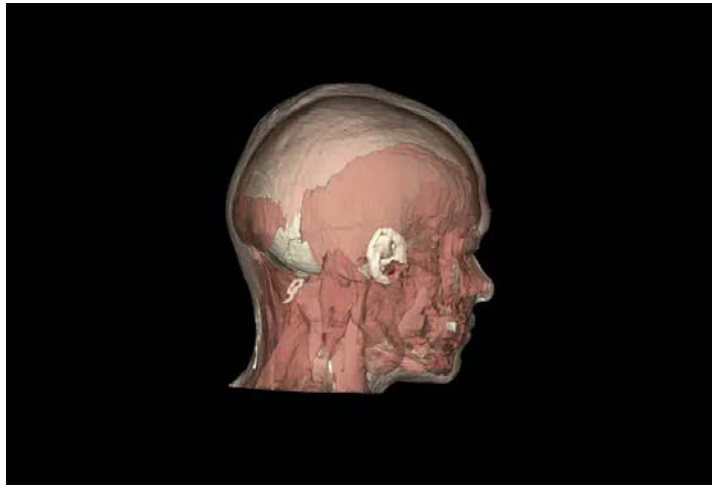




CDRH Mission

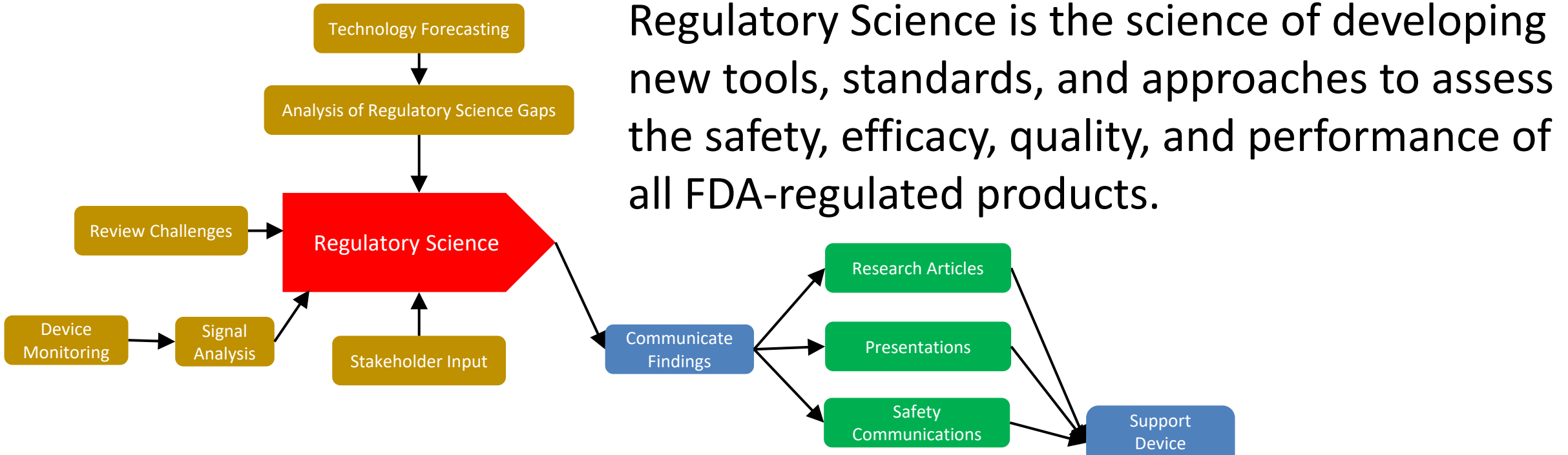
…We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee…

We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.



What is Regulatory Science?

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.



A common use of rules, conditions, guidelines for products and production methods…
A definition of terms; classification, procedures, specification, materials, performance, design, or operations…
A measurement of quality and quantity in materials, processes, products, systems, services…
A description or test methods and sampling procedures; measurement of size or strength…

An MDDT is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device. An MDDT is scientifically validated and can be qualified for use in device evaluation and to support regulatory decision-making.
https://www.fda.gov/media/87134/download

Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public.
https://www.fda.gov/industry/fda-basics-industry/guidances

Office of Science and Engineering Laboratories

- OSEL is comprised of 155 engineers, physicists, biologists, material scientists, mathematicians…

- Our objective is to:
  - Ensure readiness for innovative technologies
  - Develop test methods and facilitate optimization of devices
  - Deliver timely and accurate decisions for medical devices
  - Create accessible and understandable public health information

  – Through a culture of “4C”s: Customer first, Communication, Collaboration and Consultancy.

OSEL in Perspective

183
FEDERAL EMPLOYEES
Up to 180 visiting scientists

140 Projects
In 27 Laboratories and Program Areas

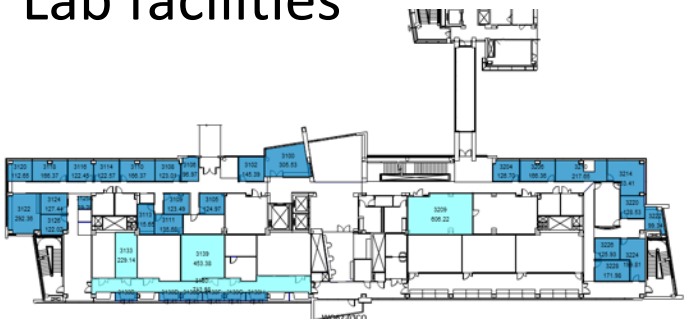
400/year
Peer reviewed presentations, articles, and other public disclosures

2,500k/year
Premarket Regulatory consults

75
Standards and conformity assessment committees

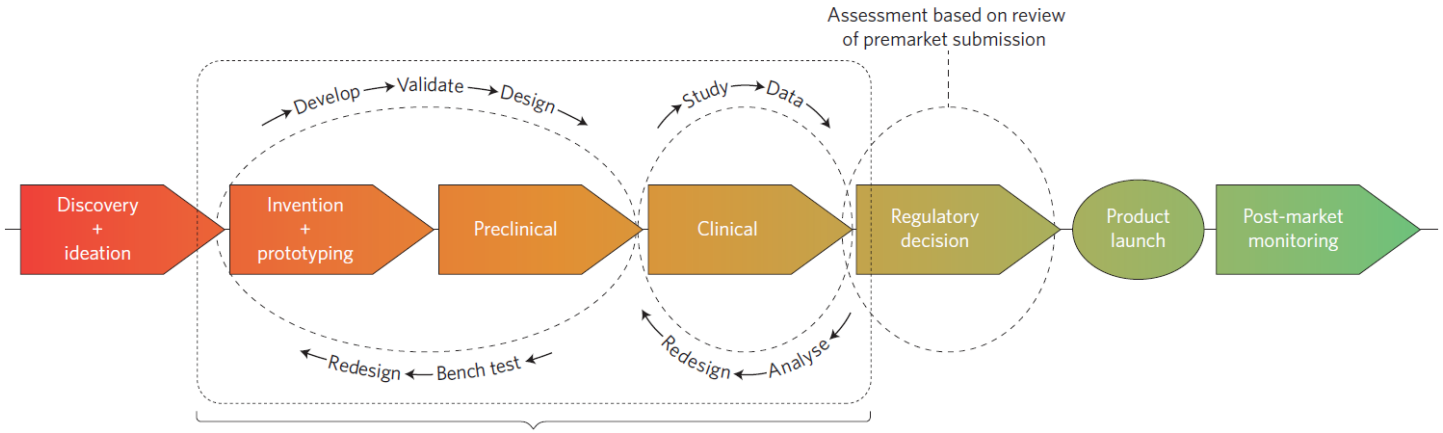
70%
Staff with post graduate degree

55,000 ft²
Lab facilities

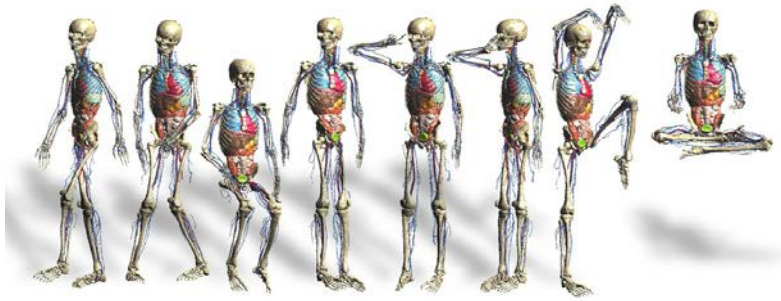


OSEL in Perspective

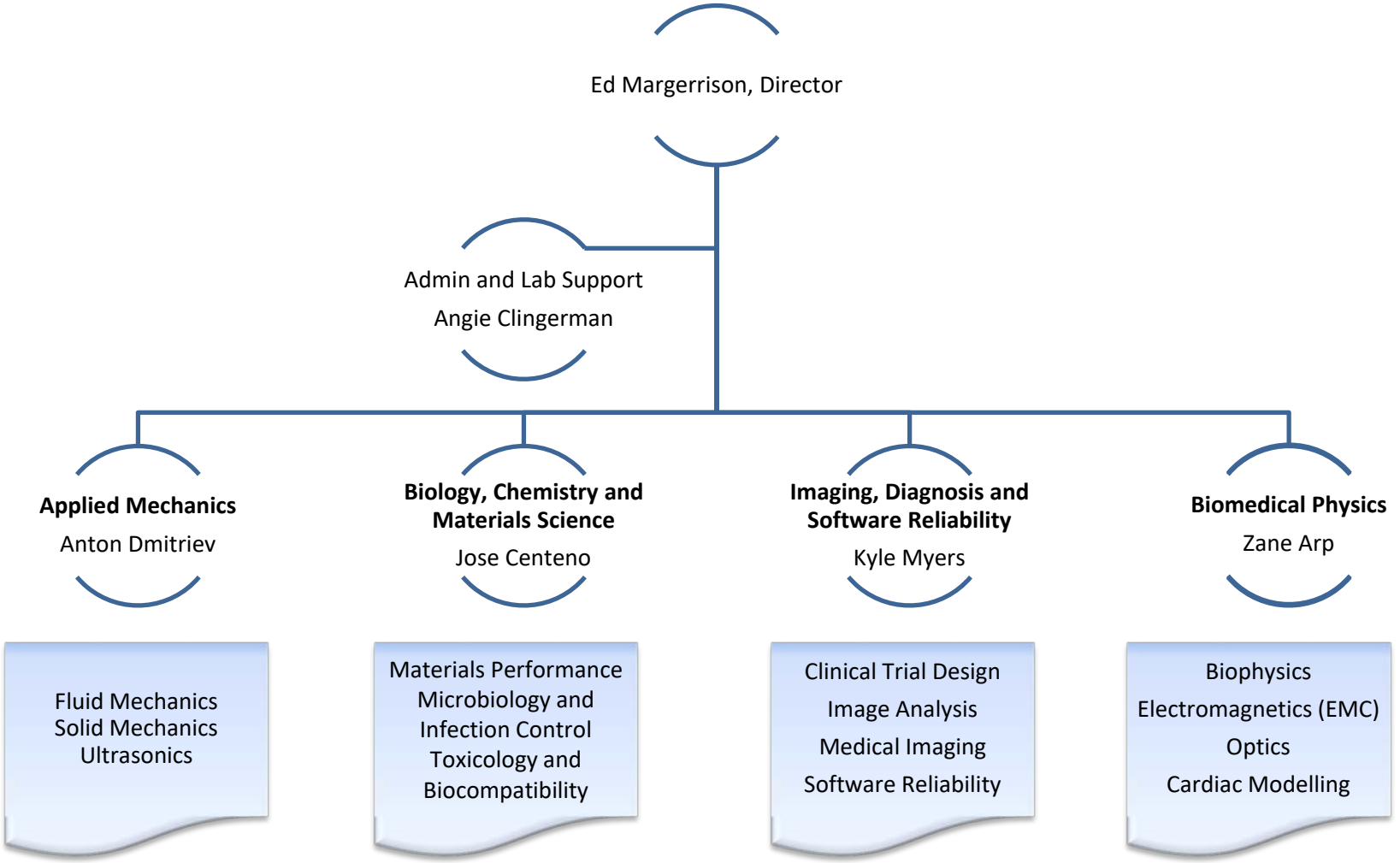
- Key role in Pre-regulatory phase technology



- AND in translational phase(s)
  - We are developing tools for a more efficient evaluation of new devices

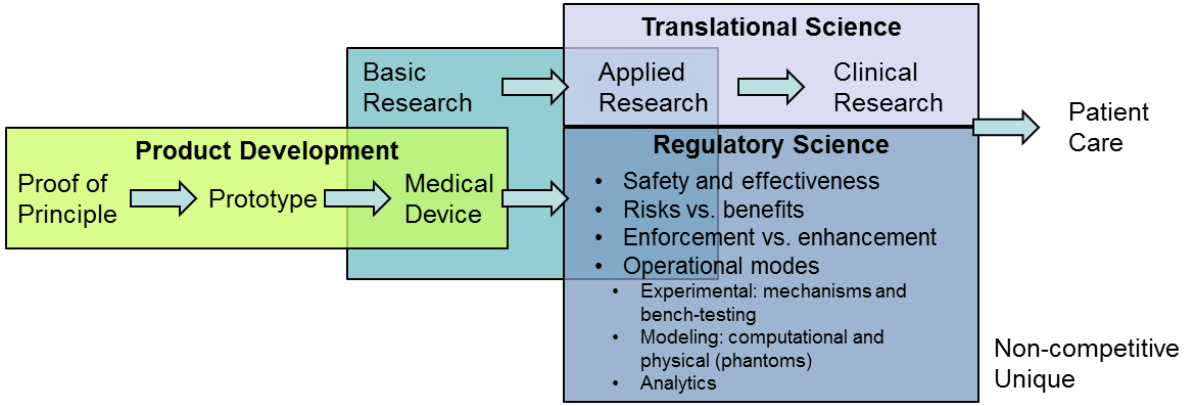


Office of Science and Engineering Labs



DBP Division Mission

The Division of Biomedical Physics (DBP) participates in the Center's mission of protecting and promoting public health by identifying and investigating the biophysical interactions between medical devices and the human body.



- EMC/wireless/electrical safety
- Neuroscience
- Optical physics
- MRI
- Functional performance and device use
- Cardiac electrophysiology
- Advanced patient monitoring and control
- Biomechanics

Contact:
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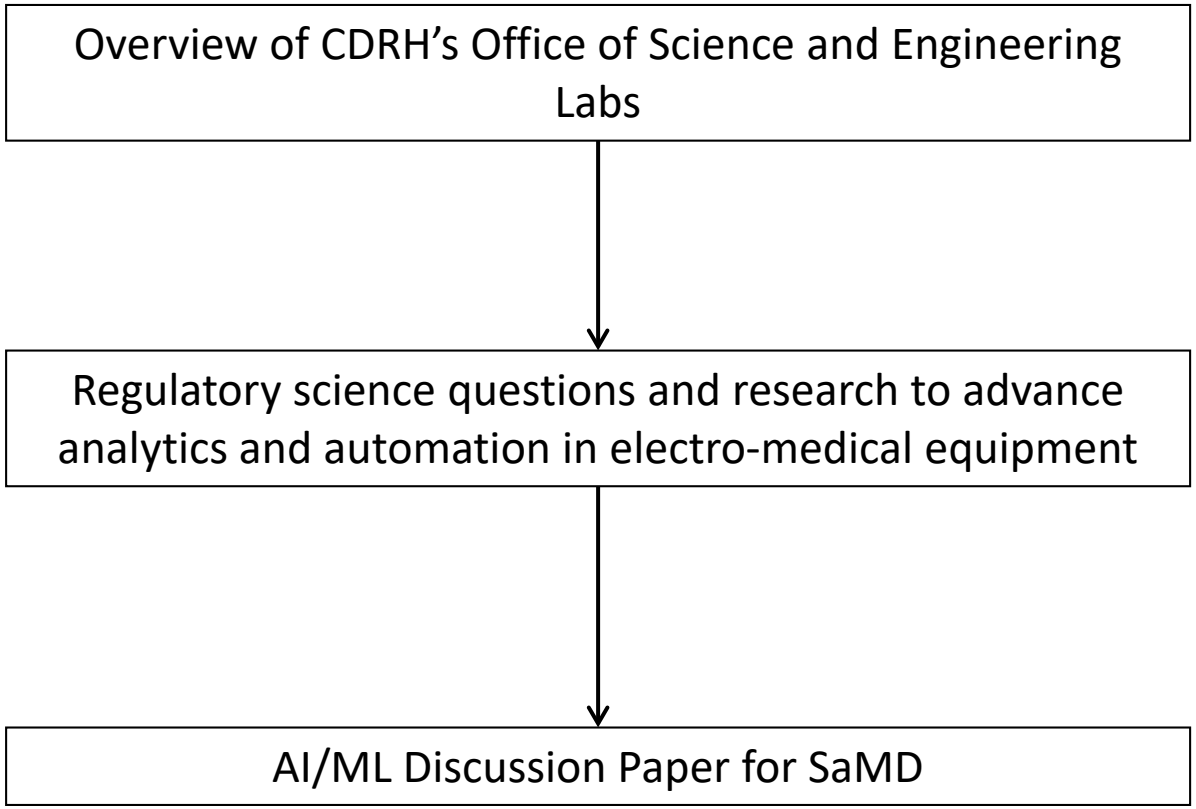
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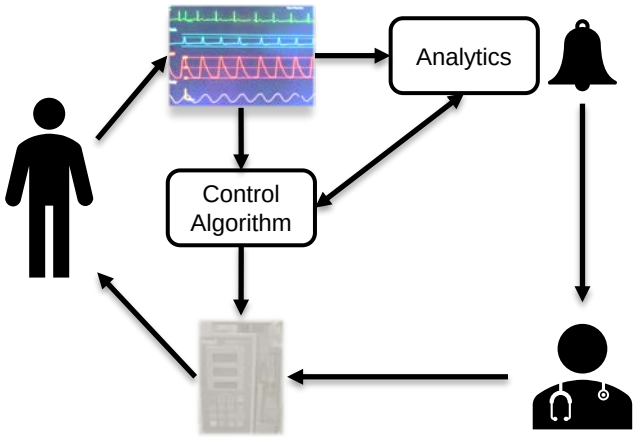
Advanced Patient Monitoring and Control

Areas of interest: Advances in analytics, automation, and interoperability in safety critical electro-medical equipment

Objective: Investigate and develop novel solutions aimed to assure the safety and effectiveness of medical devices that include advanced patient monitoring, physiological closed-loop control, or interoperable technology

Example research topics:

- Developing performance assessment methods for advanced patient monitoring algorithms
- Evaluating computational models of physiological systems for testing physiological closed-loop controlled medical devices
- Investigating research platforms and engineering methods to explore the safety implications of increasing complexity in the design and use of medical devices



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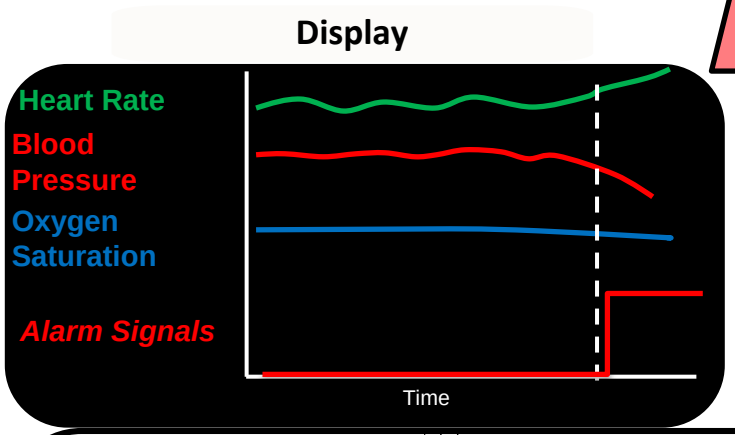
False alarms

Alarm Fatigue

Non-actionable alarms

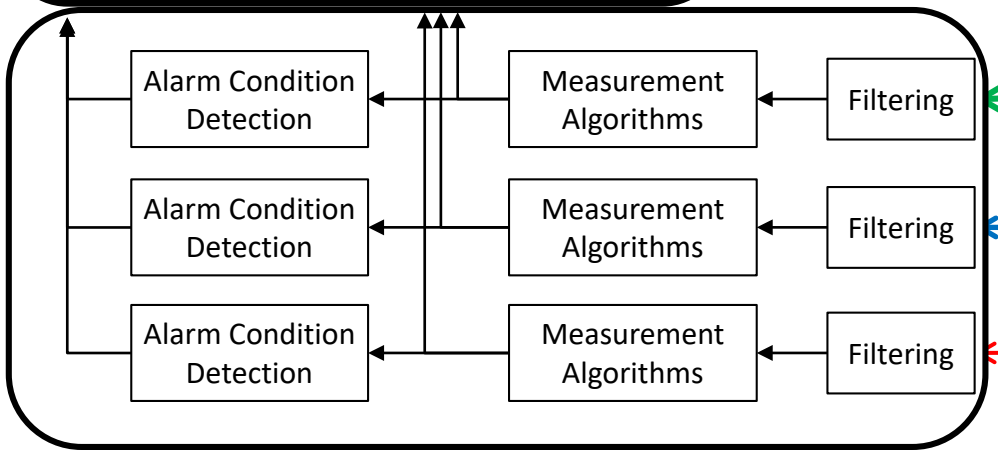
Poor interpretation of patient condition

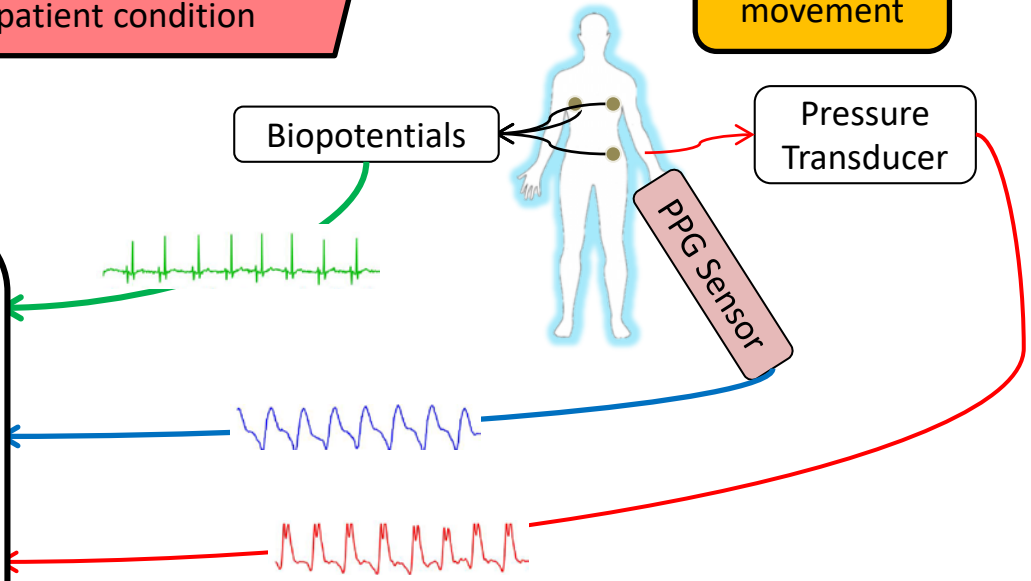
Patient movement



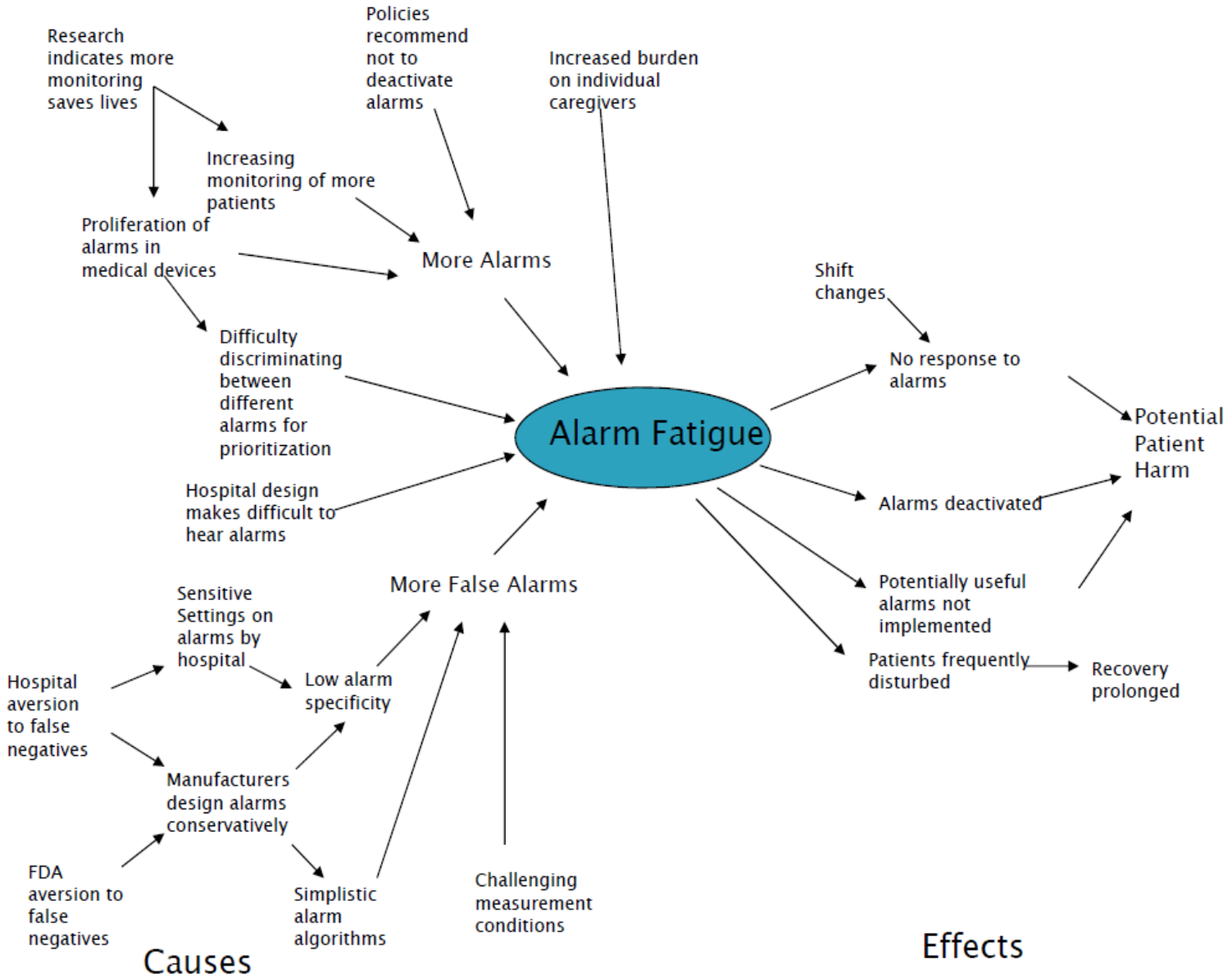
Fixed settings

No clinical context

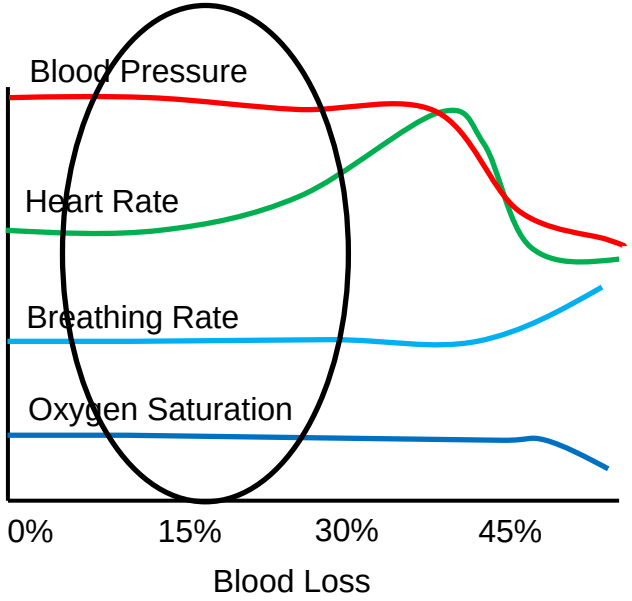


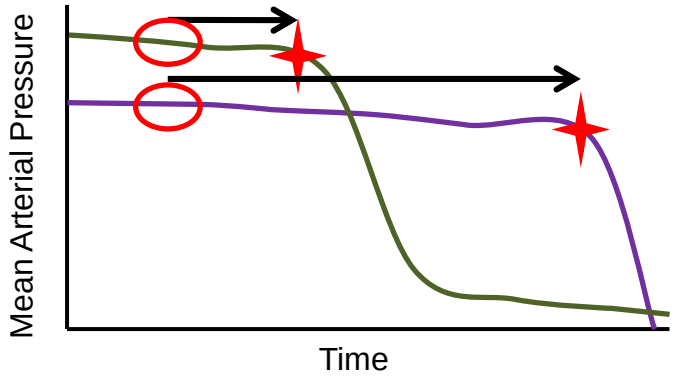


Limited use of information from multiple signals

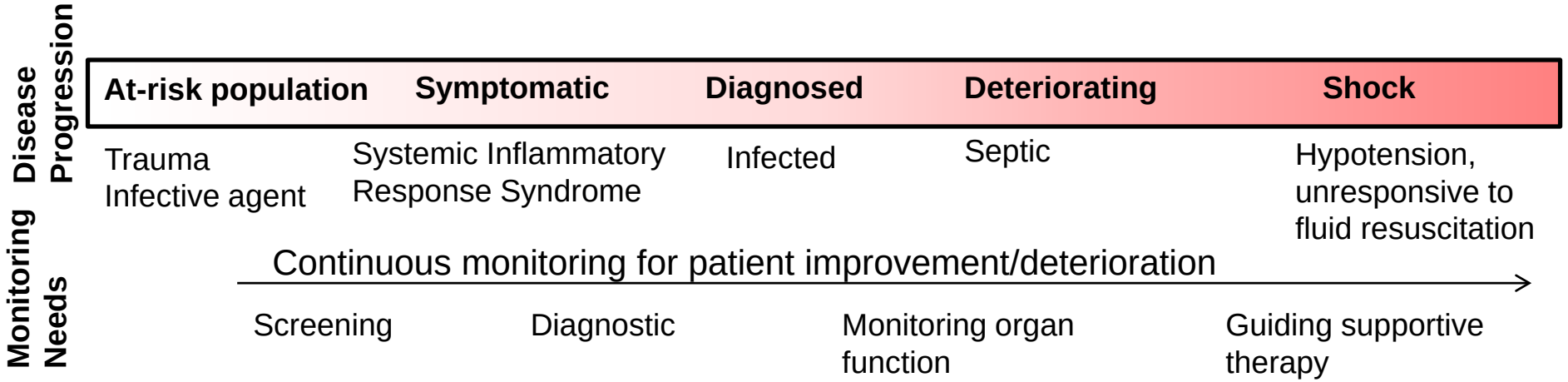

Research indicates more monitoring saves lives
Policies recommend not to deactivate alarms
Increased burden on individual caregivers
Increasing monitoring of more patients
Proliferation of alarms in medical devices
More Alarms
Shift changes
Difficulty discriminating between different alarms for prioritization
No response to alarms
Alarm Fatigue
Potential Patient Harm
Hospital design makes difficult to hear alarms
Alarms deactivated
More False Alarms
Potentially useful alarms not implemented
Sensitive Settings on alarms by hospital
Hospital aversion to false negatives
Low alarm specificity
Patients frequently disturbed
Recovery prolonged
Manufacturers design alarms conservatively
FDA aversion to false negatives
Simplistic alarm algorithms
Challenging measurement conditions
Causes
Effects

Identify Critical Events Earlier





Applications for Analytics in Patient Monitoring

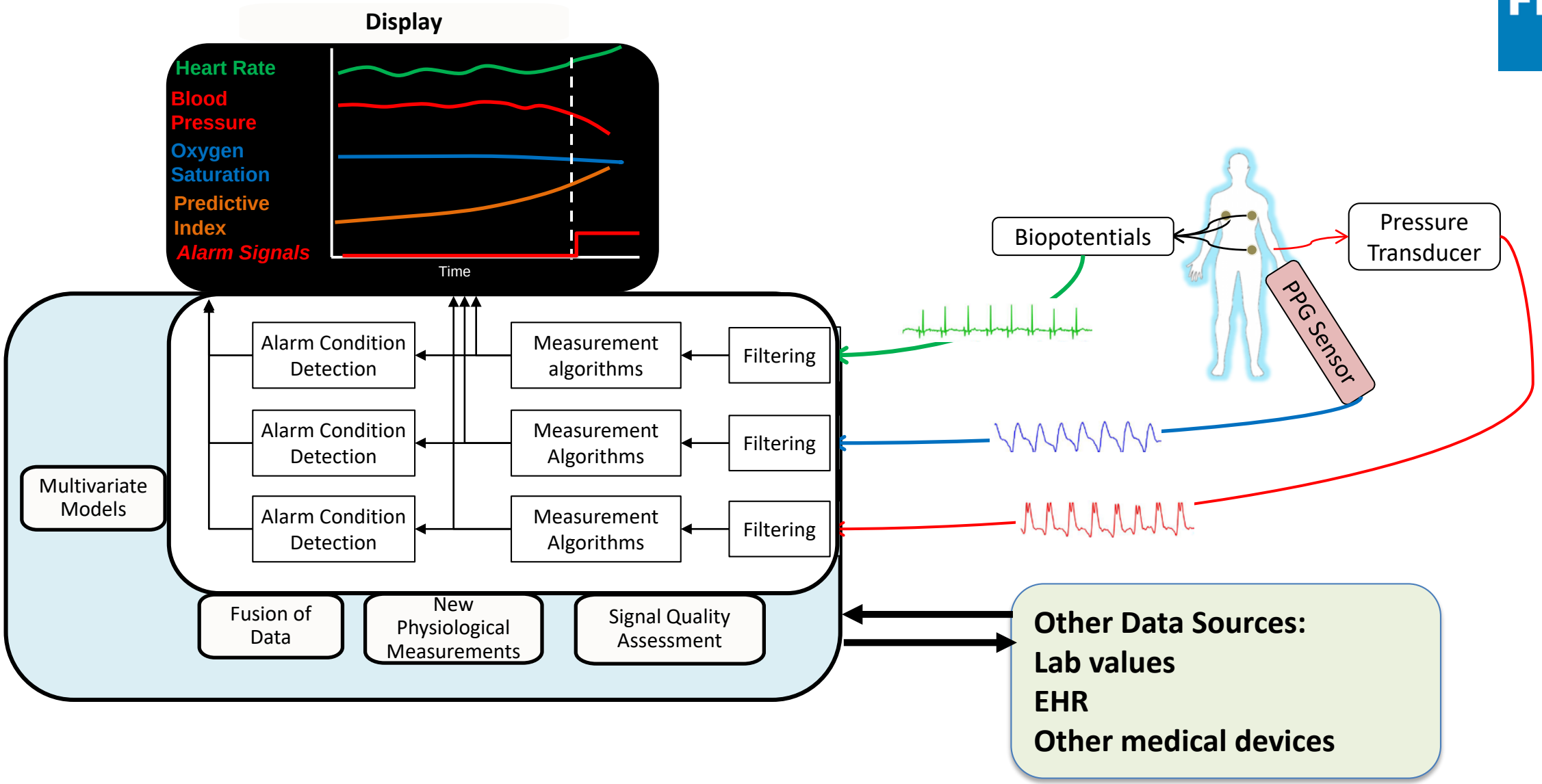


Reducing false alarms and improving measurement performance

- Alarm management – determining optimal settings for patients
  - Automatic adjustment of alarm settings by analyzing past patient data
- Signal quality assessment:
  - Signal artifact detection
  - Use of information from multiple signals
  - Identifying false positive and false negative alarm conditions

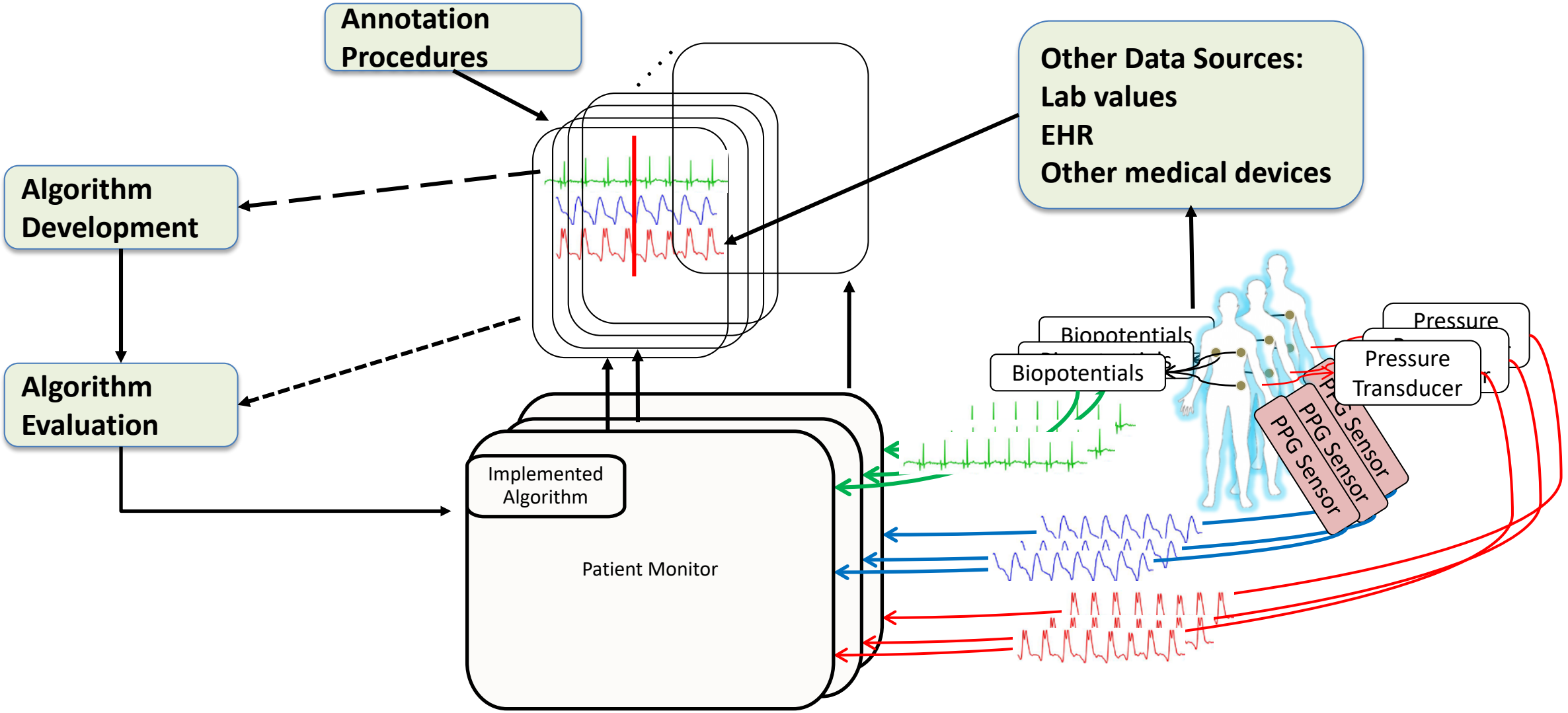
Predictive analytics for earlier identification of events

- Aid in the assessment of patient current and future condition
  - Patient risk / status indices
  - Monitors of patient deterioration
- Computer-aided detection and diagnosis
  - Detect disease signatures in physiologic waveforms
  - Measure and predict future response to therapy
- Feedback variables for physiological closed-loop systems
- Many other possibilities


Display
Heart Rate
Blood Pressure
Oxygen Saturation
Predictive Index
Alarm Signals
Time
Biopotentials
Pressure Transducer
PPG Sensor
Alarm Condition Detection
Alarm Condition Detection
Alarm Condition Detection
Measurement algorithms
Measurement Algorithms
Measurement Algorithms
Filtering
Filtering
Filtering
Multivariate Models
Fusion of Data
New Physiological Measurements
Signal Quality Assessment
Other Data Sources:
Lab values
EHR
Other medical devices

Application of Analytics & Artificial Intelligence

Creation of Patient Monitoring Databases

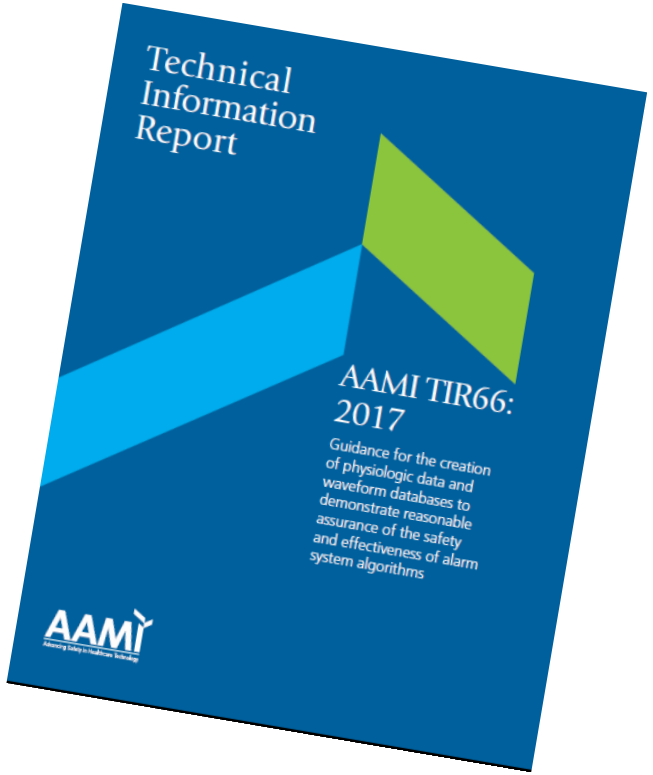


Considerations for Predictive Analytics in Patient Monitoring

- Traditionally, physiological measurements evaluated on an individual basis against established reference methods (may be clinical or bench testing)
  - According to consensus standards for many (e.g., IEC 60601-2-47:2012 for ambulatory ECG)
  - Alarms, generally, use thresholds on measurements or detect 'known' patterns in signals
- Considerations for evaluating data-driven algorithms
  - How representative is the patient population that the data is collected from?
  - How to ensure data quality?
  - Does the specific measurement device used to create the database (or settings on the monitor) have a meaningful impact on the data for the algorithm being developed?
  - What are meaningful endpoints and adequate annotation procedures?
  - How to effectively use potentially limited number of critical events for training and testing?

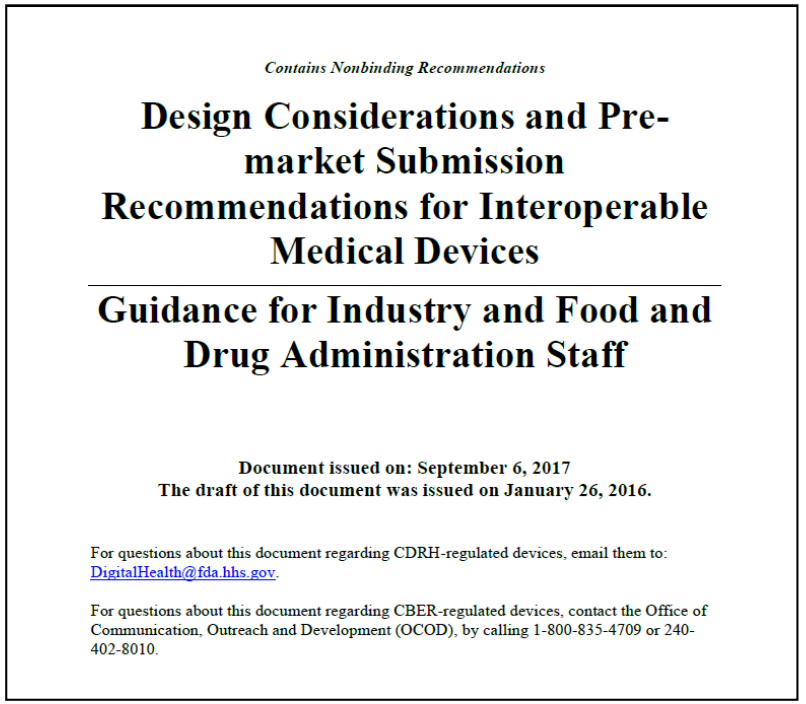
AAMI TIR66:2017 Guidance for the creation of physiologic data and waveform databases to demonstrate reasonable assurance of the safety and effectiveness of alarm system algorithms

- Recognized by FDA
- Provides guidance for:
  - Validating novel & intelligent alarm system algorithms
  - Disclosing performance of those systems
- Database requirements
  - Alignment with intended application of the algorithm
  - Population and Study Design
  - Engineering requirements
  - Annotation requirements
  - Archive requirements
- Waveform acquisition and synthesis
  - Data quality
  - Annotation processes
- Application of waveform databases to testing



Medical Device Interoperability

- Designing systems with interoperability as an objective
- Conducting appropriate verification, validation and risk management activities
- Specifying the relevant functional, performance, and interface characteristics in a user available manner such as labeling



Contains Nonbinding Recommendations

Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices

Guidance for Industry and Food and Drug Administration Staff

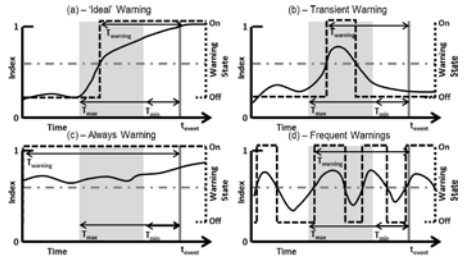
Document issued on: September 6, 2017
The draft of this document was issued on January 26, 2016.

For questions about this document regarding CDRH-regulated devices, email them to: DigitalHealth@fda.hhs.gov.

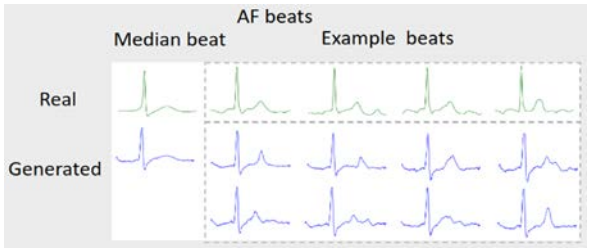
For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD), by calling 1-800-835-4709 or 240-402-8010.

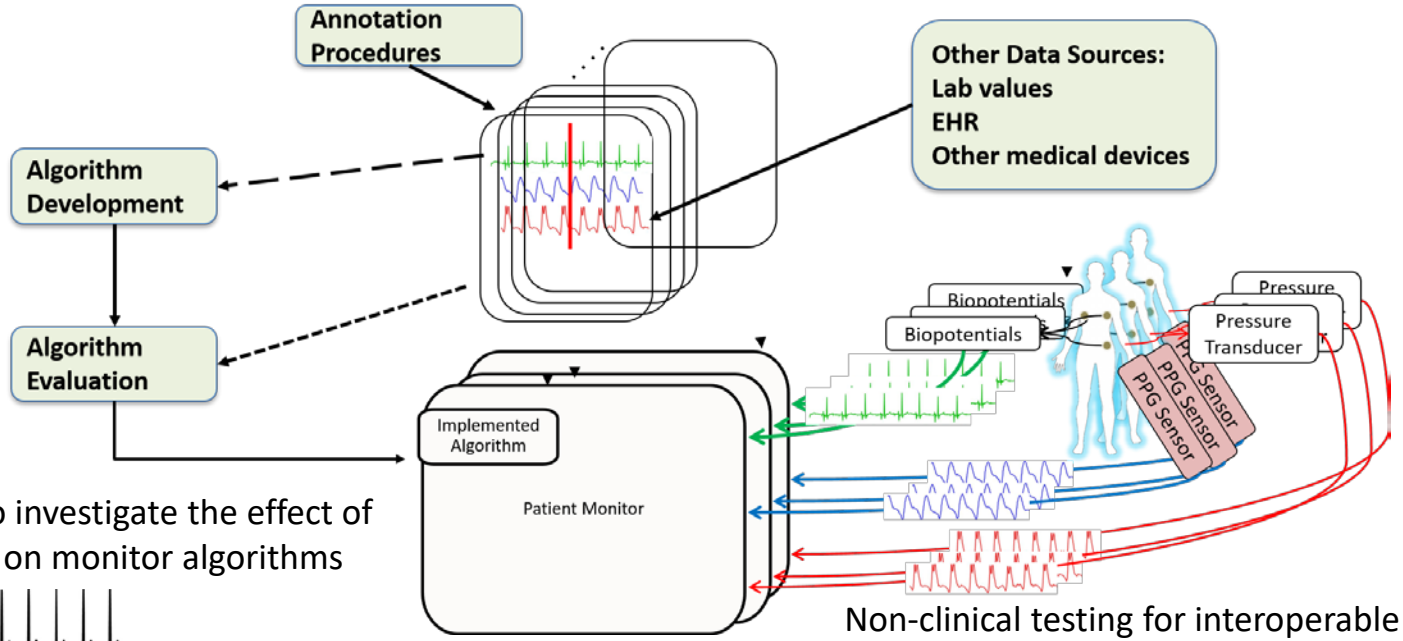
Patient Monitoring Regulatory Science in OSEL/DBP

Use of patient monitoring databases to evaluate predictive alarm algorithms and effects on alarm fatigue

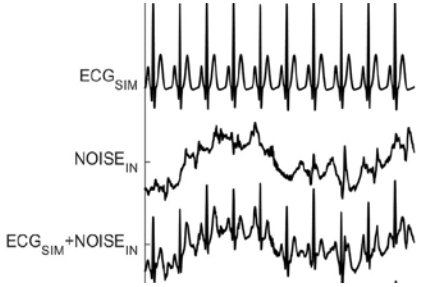


Simulating physiologic signals for efficient use of databases in algorithm design

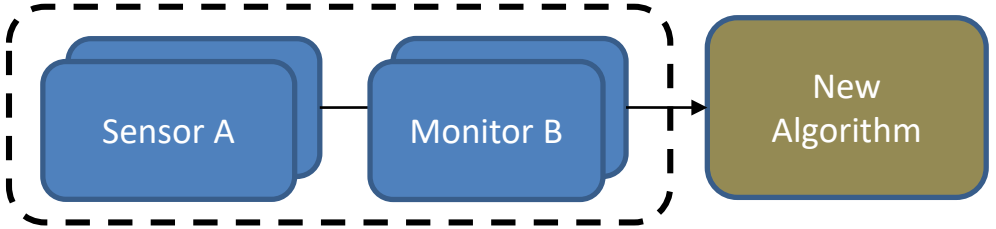




Computational methods to investigate the effect of noise and motion artifacts on monitor algorithms

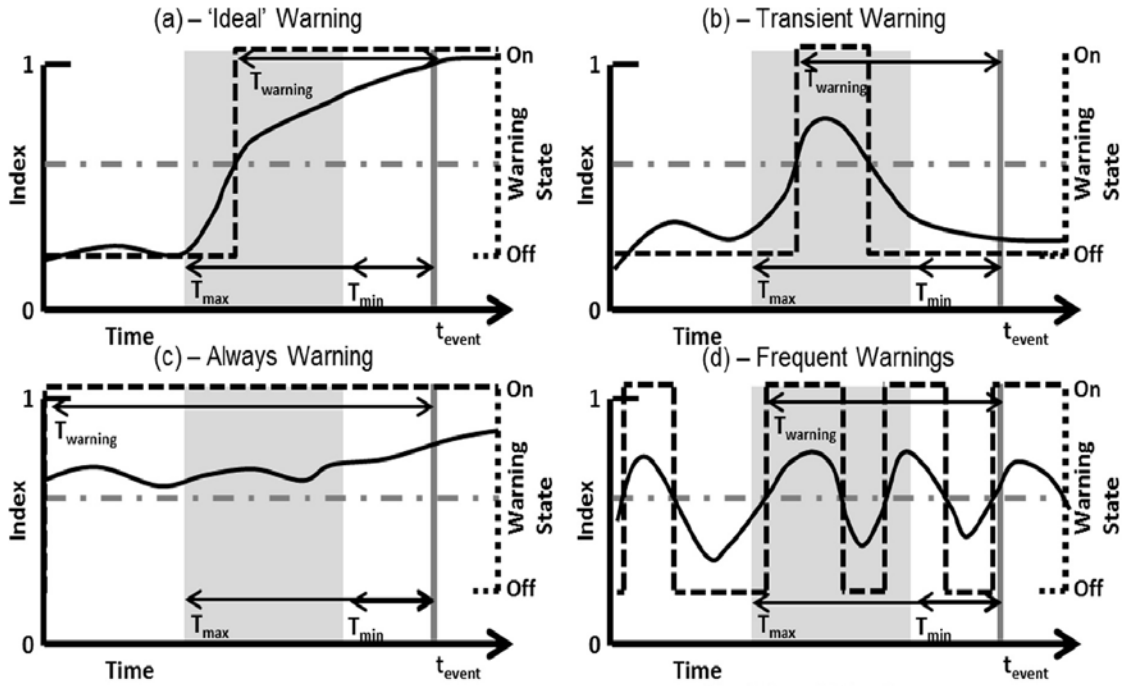


Non-clinical testing for interoperable monitoring systems to test performance with different physiologic signal acquisition systems



Characterizing Patterns of Indices Leading up to Critical Event

- Novel index with an alarm system may have a variety of patterns prior to a critical event
- How should performance be evaluated to provide meaningful and understandable information?
  - Performance within clinically relevant time period before event
  - Distribution of warning times
  - Whether the alarm condition is present until event
  - Number of false alarms / event



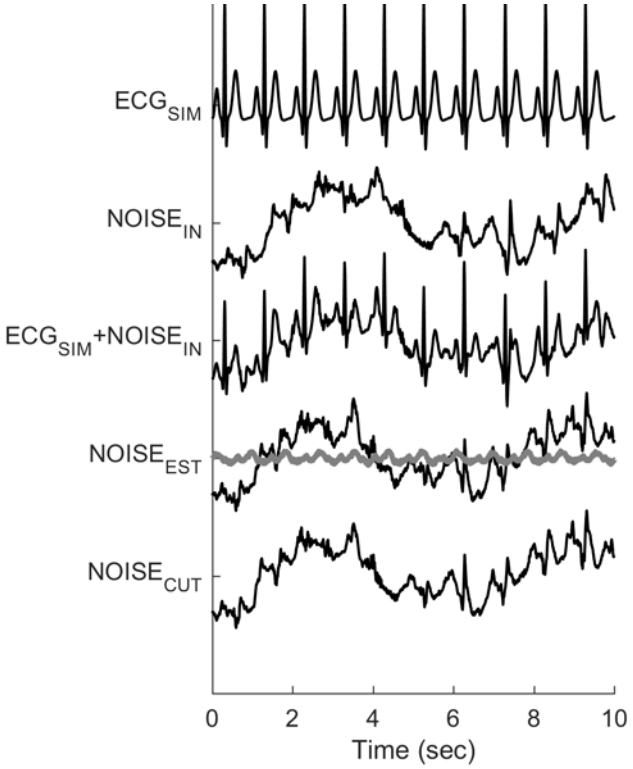
Extracting noise from electrocardiogram recordings for robust algorithm testing

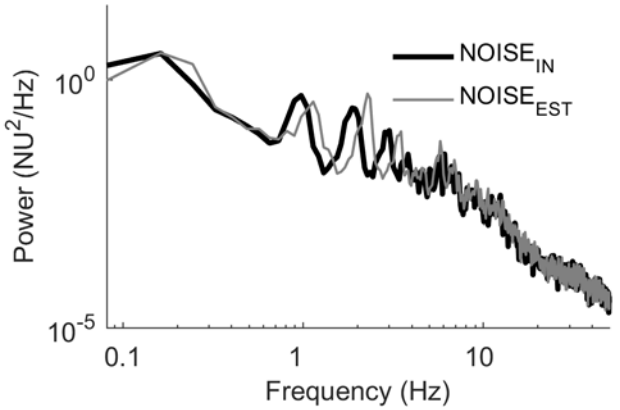
- ANSI/AAMI EC57 includes testing ECG analysis algorithms across range of SNRs by applying 3 recorded noise records
- Same noise records used for all devices – unclear if these are adequate and representative for novel portable devices

Approach

- Developed method to enable noise component to be extracted from ECG signal
  - Representative noise records can then be added to annotated databases

A method to extract realistic artifacts from electrocardiogram recordings for robust algorithm testing



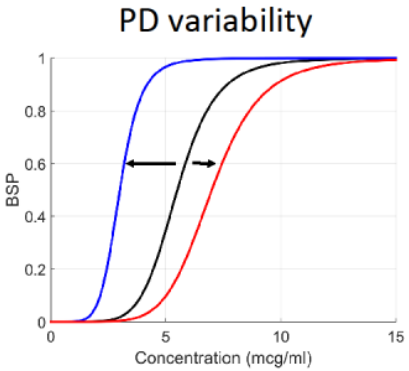


Hazardous Situations for a Physiologic Closed-Loop Controlled Device

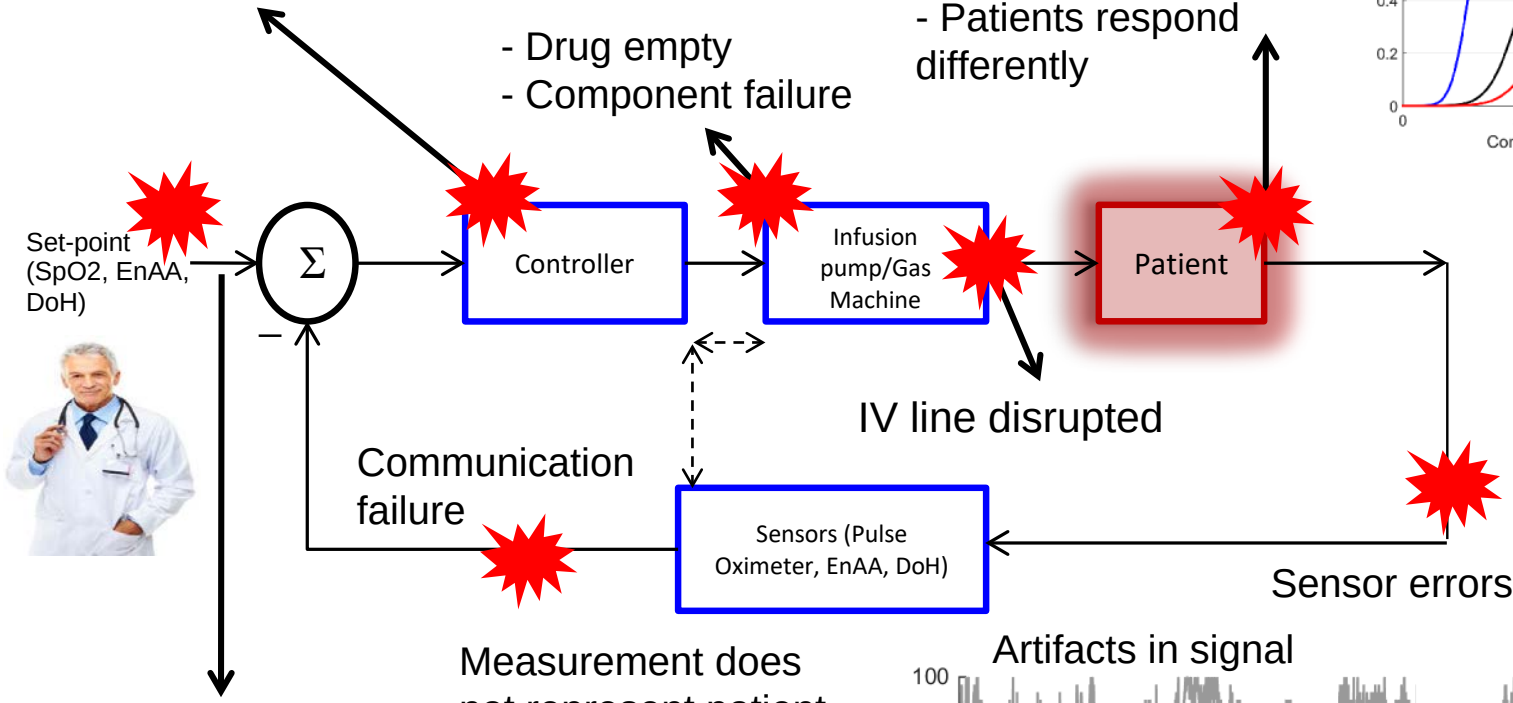
Controller:
- May leads to unstable system
- Not robust to different patient responses
- May not recognize change in patient response

- Drug empty
- Component failure

- Within patient changes
- Patients respond differently

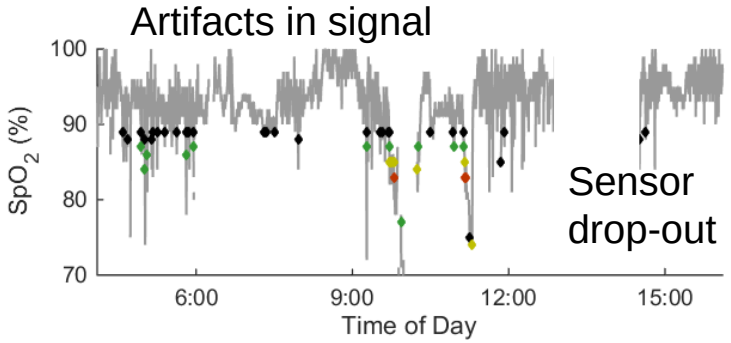


Purdon, FDA PCLC Workshop 2015.



Usability errors:
- Wrong patient information
- Wrong drug concentration
- Over-reliance on device

Measurement does not represent patient condition



Medical Device Evaluation

- Comprehensive evaluation of a marketing application for a therapeutic medical device typically includes **valid scientific evidence** from some combination of **four possible types of models**: animal, bench, computational, and human.
- Each model has its strengths and limitations for predicting clinical outcomes.
- Computational evidence has many potential uses for physiologic closed-loop controlled devices

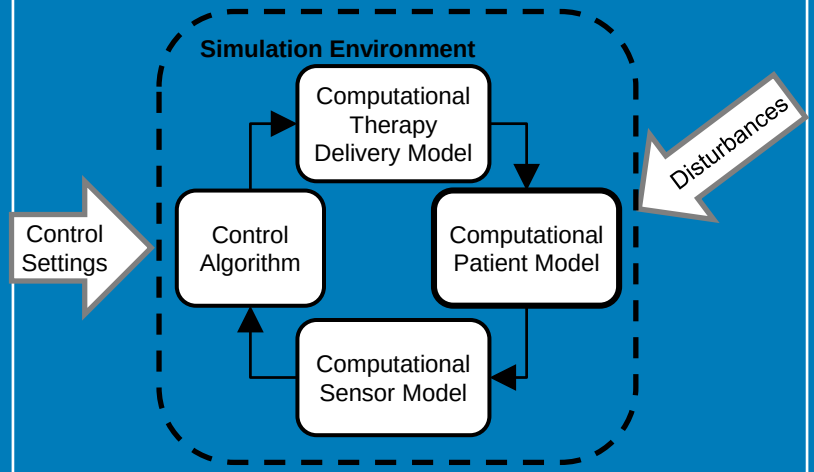
Uses of Modeling for Physiologic Closed-loop Controlled Devices

Model-Based Design

Established field of engineering
Enables quantitative assessment of system
Analytical stability
Transparency
Lends itself well to model-based evaluation

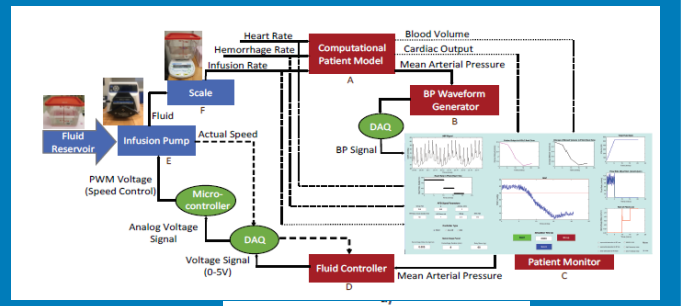
Complete In Silico Testing

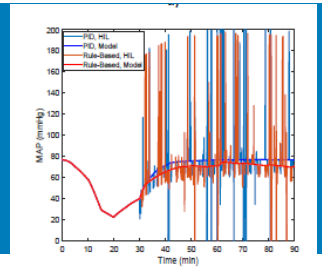
Ability to produce a variety of physiological conditions (in silico patients)
Modularity



Hardware-in-the-Loop Evaluation

Enables real time testing with device hardware
Allow for evaluation of worst-case scenarios
Stress testing
Scenarios not easy to replicate in clinical setting





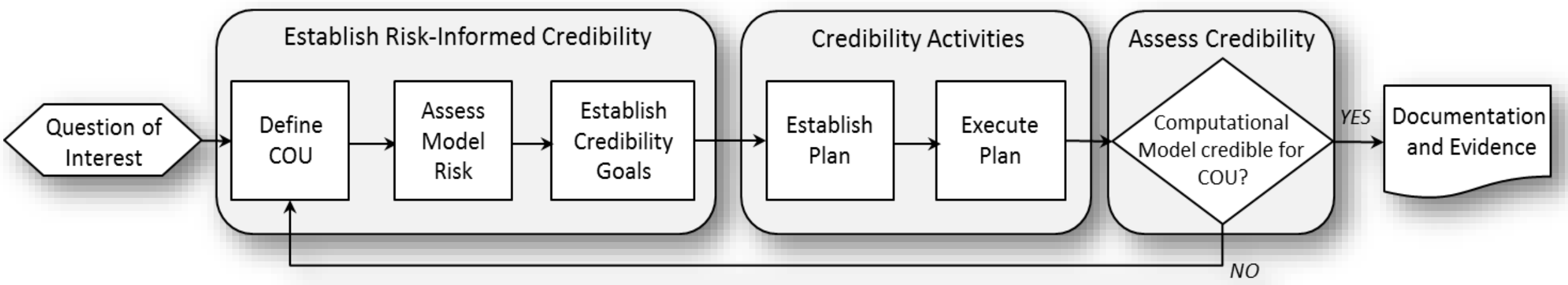
Evaluation of Fluid Resuscitation Control Algorithms via a Hardware-in-the-Loop Test Bed

Hossein Mirinejad*, Bahram Parvinian, Margo Ricks, Yi Zhang, Sandy Weininger, Jin-Oh Hahn, and Christopher G. Scully

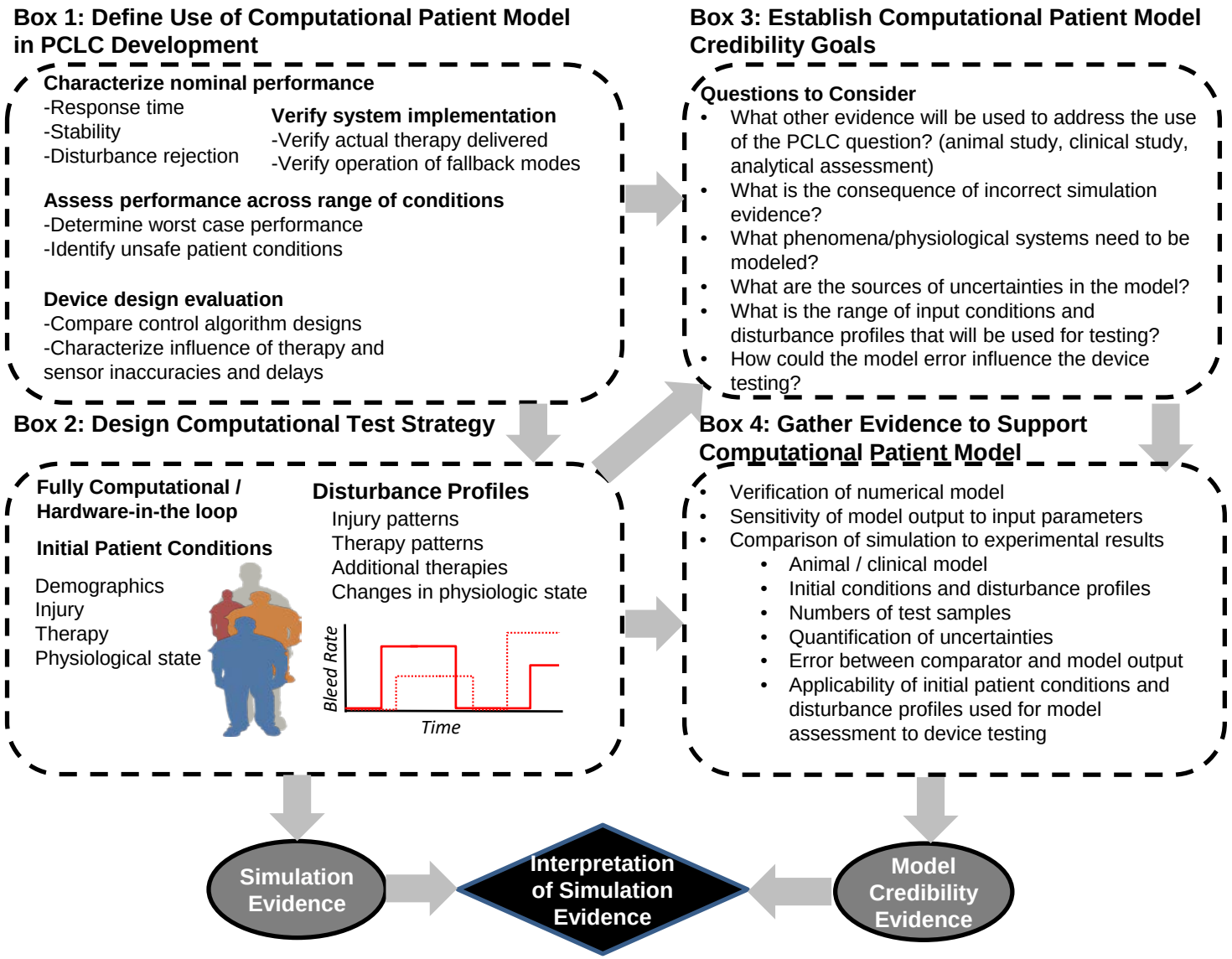
Challenges for computational testing of physiologic closed-loop controlled devices

- Need physiological models that lend themselves to control system design
  - Need to be simple enough for design of controller but accurate enough to capture the physiology of interest
  - Physiological systems have many mechanisms that are unknown and difficult to model
- Variability in physiological systems from one patient to another, and within patient
  - 747s are manufactured to be similar with similar properties/response
- High degree of cross-coupling between physiological systems
  - cardiovascular-respiratory-renal
- High degree of versatility for a single physiological system
  - Function of respiratory system is for oxygenation and ventilation, but it also helps to cool the body
- **How to demonstrate credibility of computational modeling and simulation results in the evaluation of physiologic closed-loop controlled devices?**

ASME V&V40 Framework Overview



The ASME V&V 40 standard outlines a framework for making risk-informed determinations as to whether a CM&S is credible for decision-making for a specified context of use.

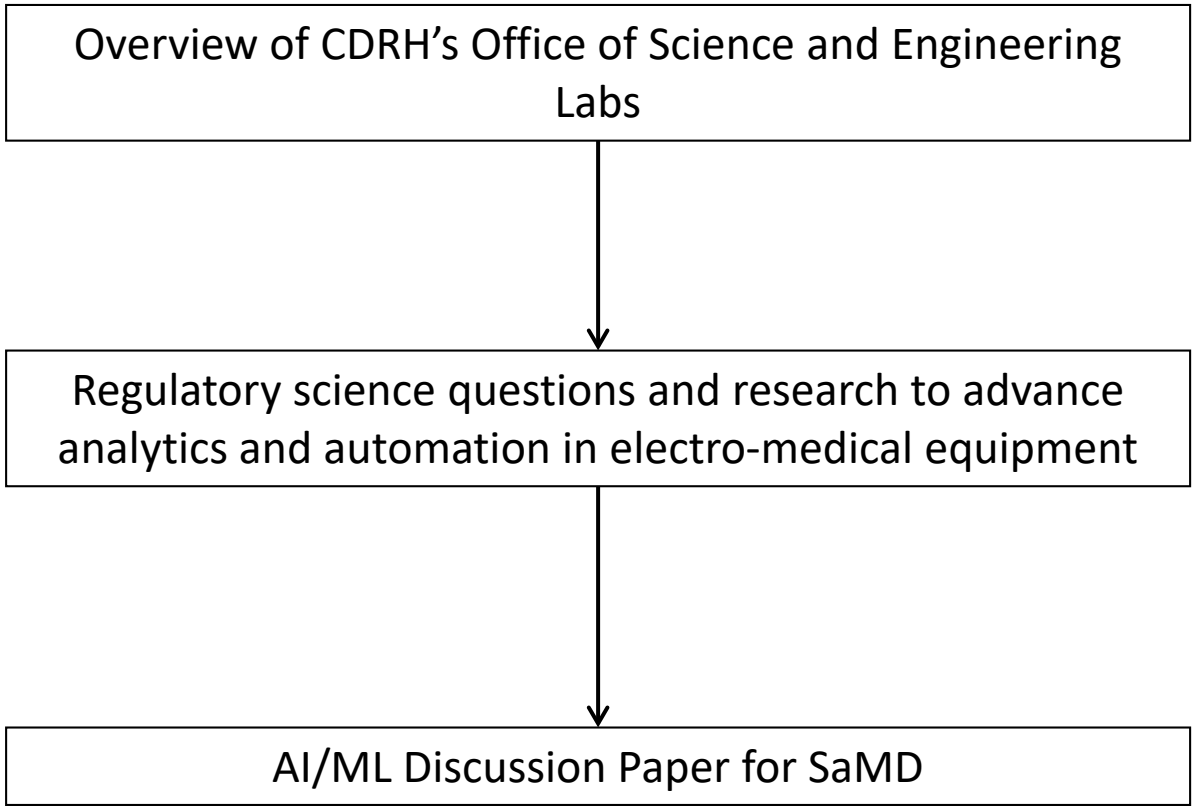


frontiers in Physiology

REVIEW
published: 26 March 2019
doi: 10.3389/fphys.2019.00220

Credibility Evidence for Computational Patient Models Used in the Development of Physiological Closed-Loop Controlled Devices for Critical Care Medicine

Bahram Parvinian, Pras Pathmanathan, Chathuri Daluwatte, Farid Yaghouby, Richard A. Gray, Sandy Weininger, Tina M. Morrison and Christopher G. Scully*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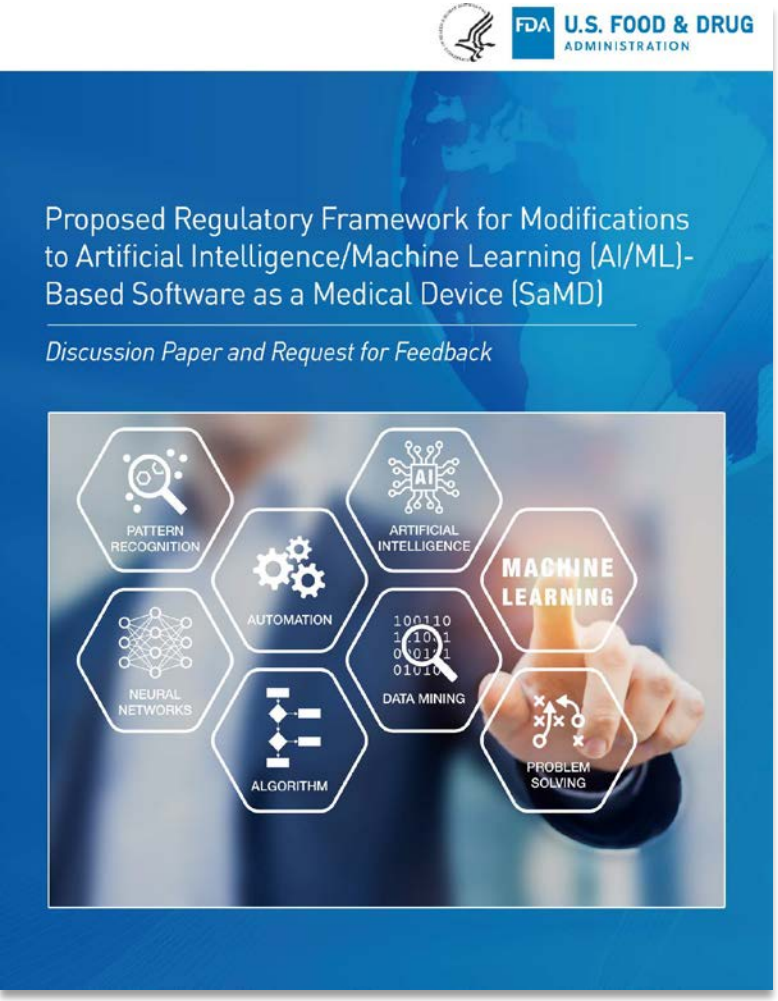
Regulatory science questions and research to advance analytics and automation in electro-medical equipment
AI/ML Discussion Paper for SaMD

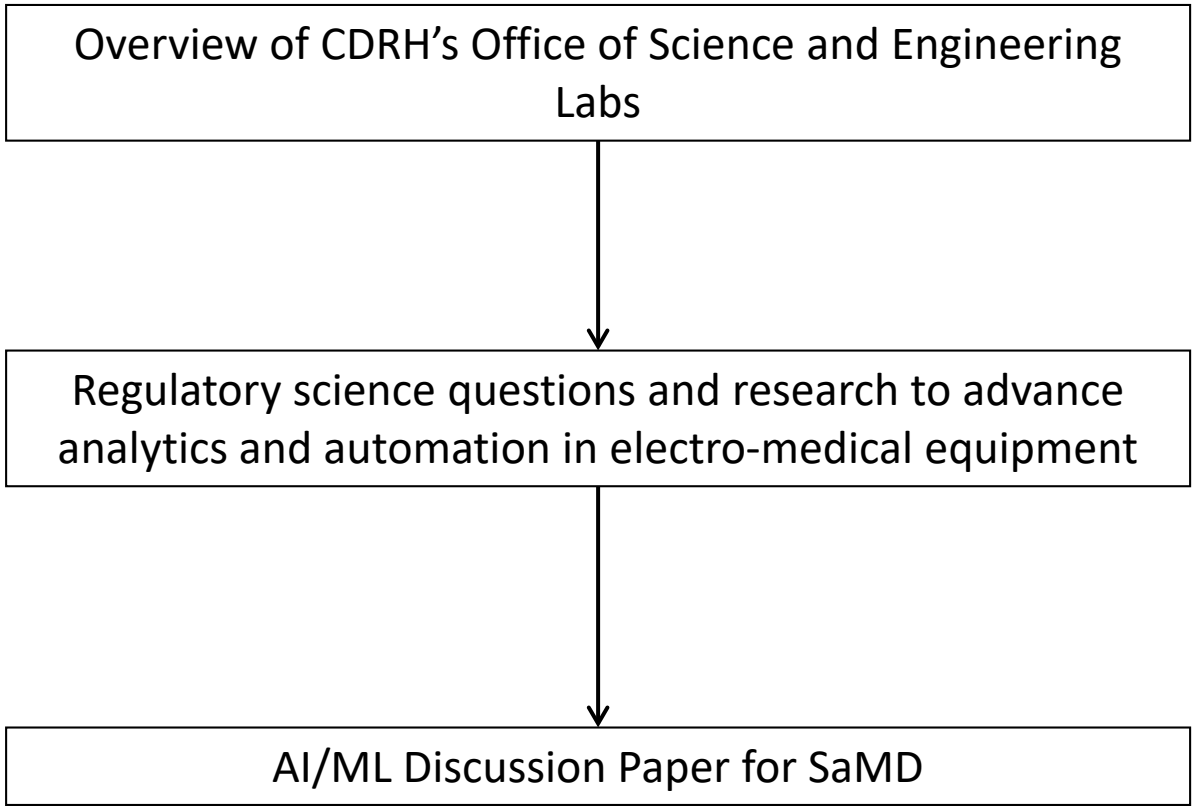
AI/ML Discussion Paper



"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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And Devices

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