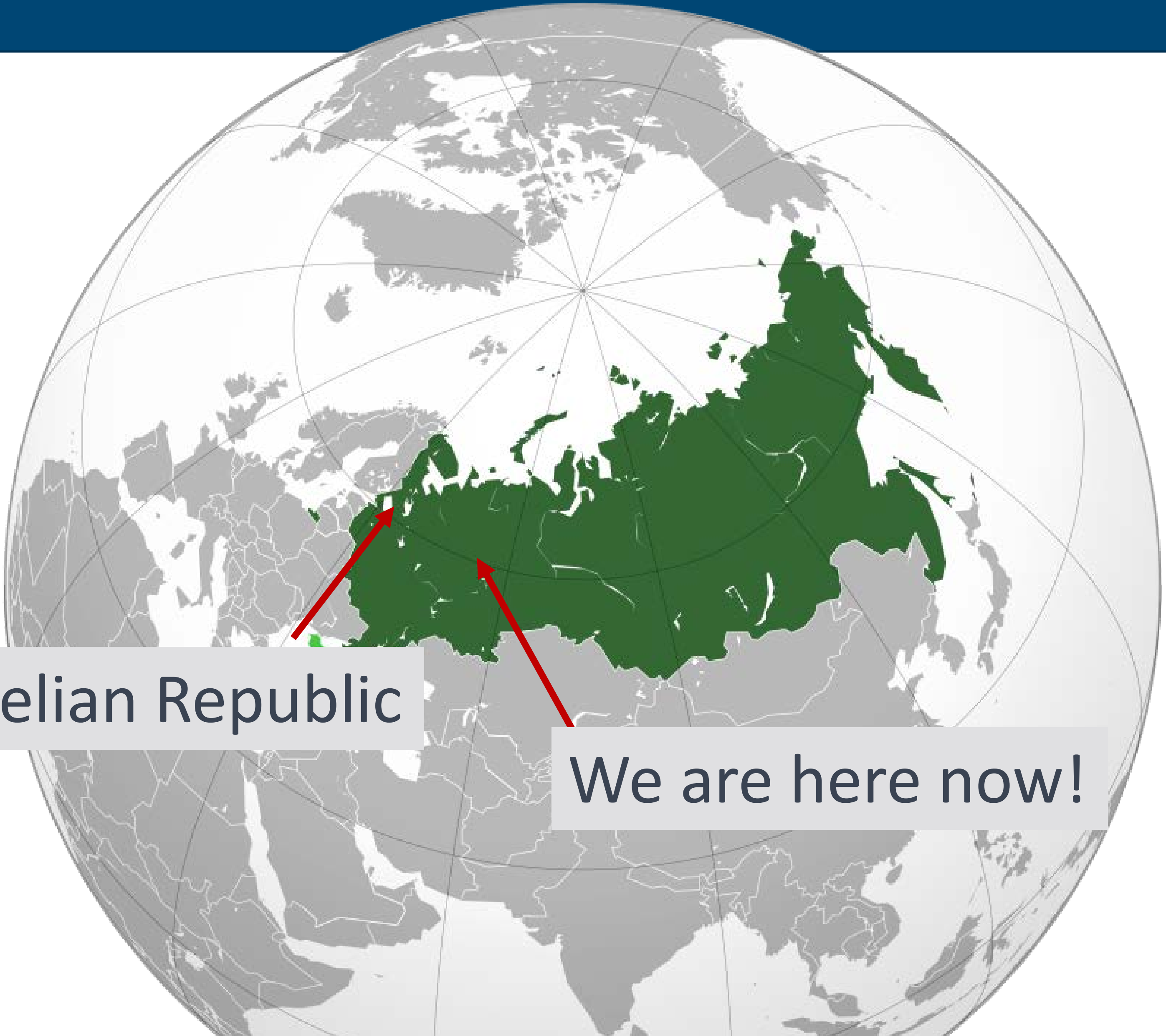
PREPARATION AND CONDUCT CLINICAL TRIALS FOR AN ARTIFICIAL INTELLIGENCE-BASED CLINICAL DECISION SUPPORT SYSTEM

Denis Gavrilov,
Chief Karelia Republic Regional Office,
Russian Society of Cardiology.

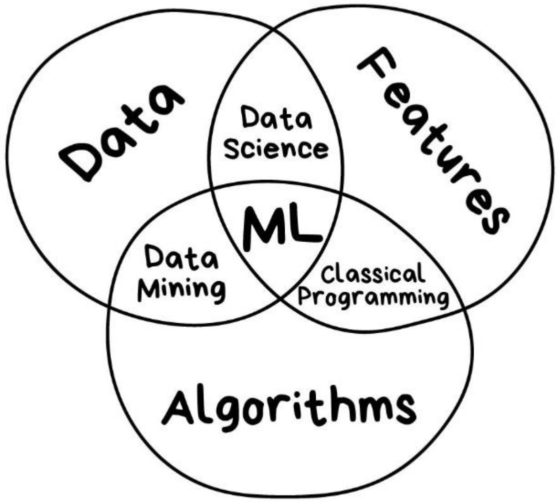
IMDRF/DITTA joint workshop «Artificial Intelligence in Healthcare»

Our working group from…



ML Specialists

Cardiologists



IT Specialists

Challenges of Applying ML in Healthcare

- quality date sets
- evidence of clinical efficacy and safety of machine learning software

TABLE of CONTENTS

BREAKING NEWS ABOUT ARTIFICIAL INTELLIGENCE IN HEALTHCARE IS BECOMING THE NORM OF OUR LIFE

WORLDPHARMANEWS

SMi Presents the
Inaugural Conference...

Pharmaceutical Manufacturing &

Circulation

ORIGINAL RESEARCH ARTICLE

Machine Learning to Predict the Likelihood of Acute Myocardial Infarction

Martin P. Than, MBBS*
John W. Pickering, PhD*
Yader Sandoval, MD
Anoop S.V. Shah, MBChB, PhD
Athanasios Tsanas, PhD
Fred S. Apple, PhD
Stefan Blankenberg, MD
Louise Cullen, MBBS, PhD
Christian Mueller, MD
Johannes T. Neumann, MD
Raphael Twerenbold, MD

BACKGROUND: Variations in cardiac troponin concentrations by age, sex, and time between samples in patients with suspected myocardial infarction are not currently accounted for in diagnostic approaches. We aimed to combine these variables through machine learning to improve the assessment of risk for individual patients.

METHODS: A machine learning algorithm (myocardial-ischemic-injury-index [MI³]) incorporating age, sex, and paired high-sensitivity cardiac troponin I concentrations, was trained on 3013 patients and tested on 7998 patients with suspected myocardial infarction. MI³ uses gradient boosting to compute a value (0–100) reflecting an individual's likelihood of a diagnosis of type 1 myocardial infarction and estimates the sensitivity, negative predictive value, specificity and positive predictive value for that individual. Assessment was

ESC Congress
Paris 2019
31 August - 4 September

MACHINE LEARNING IN CARDIOLOGY: ESC CONGRESS 2019 RESULTS

Artificial Intelligence for ACC and CAD

Artificial intelligence M-health

Artificial Intelligence for Arrhythmias

Topic	n	%
ECG	6	40
Arrhythmias	2	13
Echocardiography	2	13
Text Speech Recognition	2	13
Predictions CVD, IM	2	13
Methodology ML	1	6

OTHER EXAMPLES ML IN CARDIOLOGY

- Mortality prognosis and risk stratification in heart failure (Ortiz et al. 1995; Atienza et al. 2000)
- Echocardiographic imaging analysis (Narula et al. 2017)
- Prediction on the development of atrial fibrillation (Kolek et al. 2016)
- Prediction of cardiovascular event risk (Pavlou et al. 2015)
- Prediction of in-stent restenosis from plasma metabolites (Cui et al. 2017)
- Real-time patient-specific ECG classification (Kiranyaz, Ince, and Gabbouj 2015)
- Automatic tissue classification of coronary artery (Abdolmanafi et al. 2017)
- Early detection of heart failure onset (Choi et al. 2016)

digital diagnostics
digital predictions

"clinical trials" - a developed and planned systematic study, including with the participation of a person as a subject to assess the safety and effectiveness of a medical device

Regulatory Documents

- Law and Decree of the Russian Federation

- Recommendations: clinical trials of software based on intelligent technologies (radiation diagnostics), 2019

- Software as a Medical Device (SaMD): Clinical Evaluation. IMDRF Final Document, 2017.

Clinical Validation Approaches

- prospective
- retrospective using patient data
- *in silico* - computer simulation experiment
- notification

HEALTH RISKS from Medical Devices

- class 1 - medical devices with a low degree of risk
- class 2a - medical devices with an average degree of risk
- class 2b - medical devices with a increased degree of risk
- class 3 - medical devices with a high degree of risk

Application Criteria:

- duration of use;
- invasiveness;
- the presence of contact with the human body or relationship with him;
- a method for introducing a medical device into the human body (through anatomical cavities or surgically);
- application for vital organs;
- use of energy sources.

e.g: a model predicting the risk of death from CVD belongs to class 1

HEALTH RISKS from Medical Devices

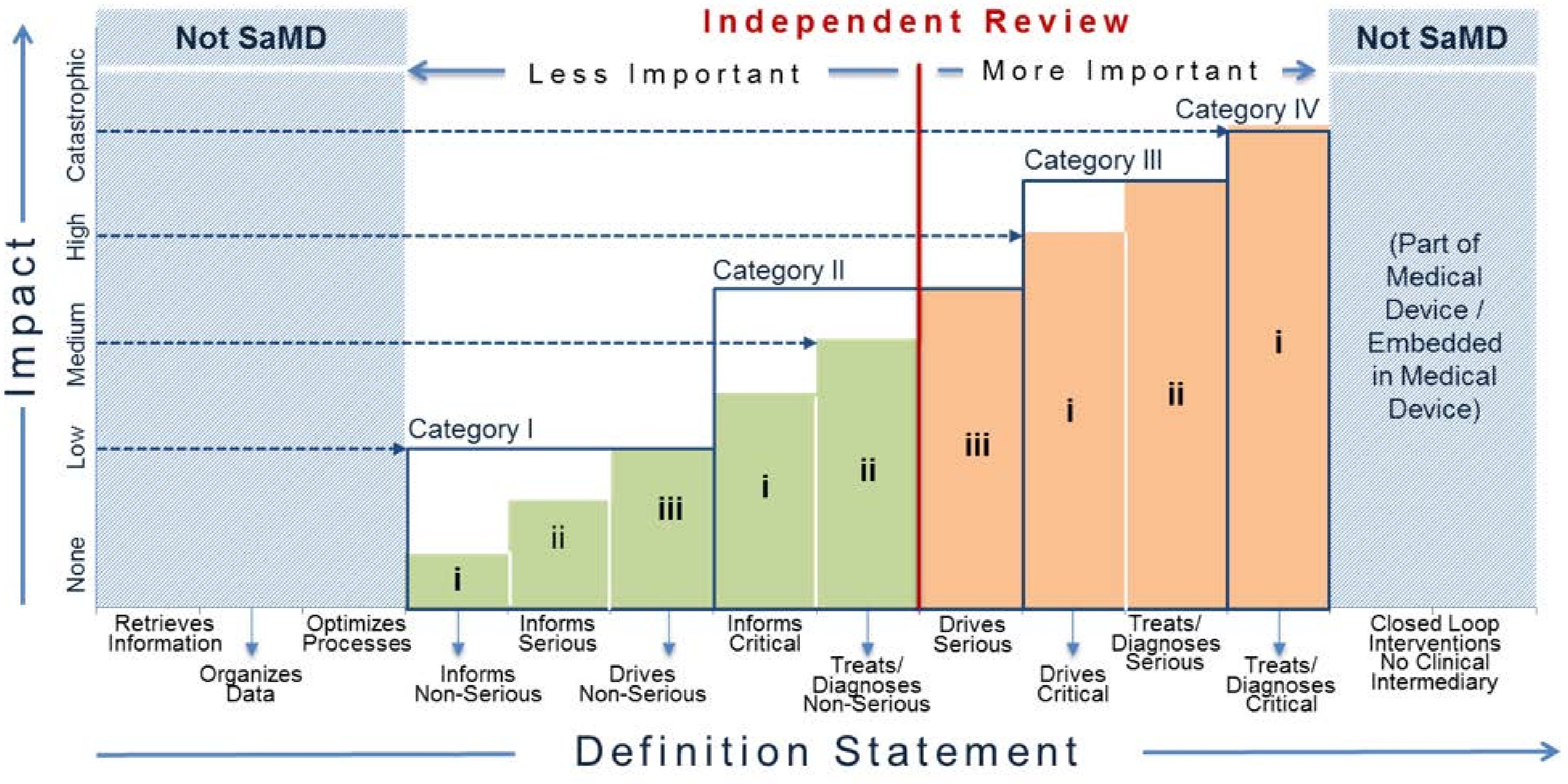
SaMD Definition Statement

- 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

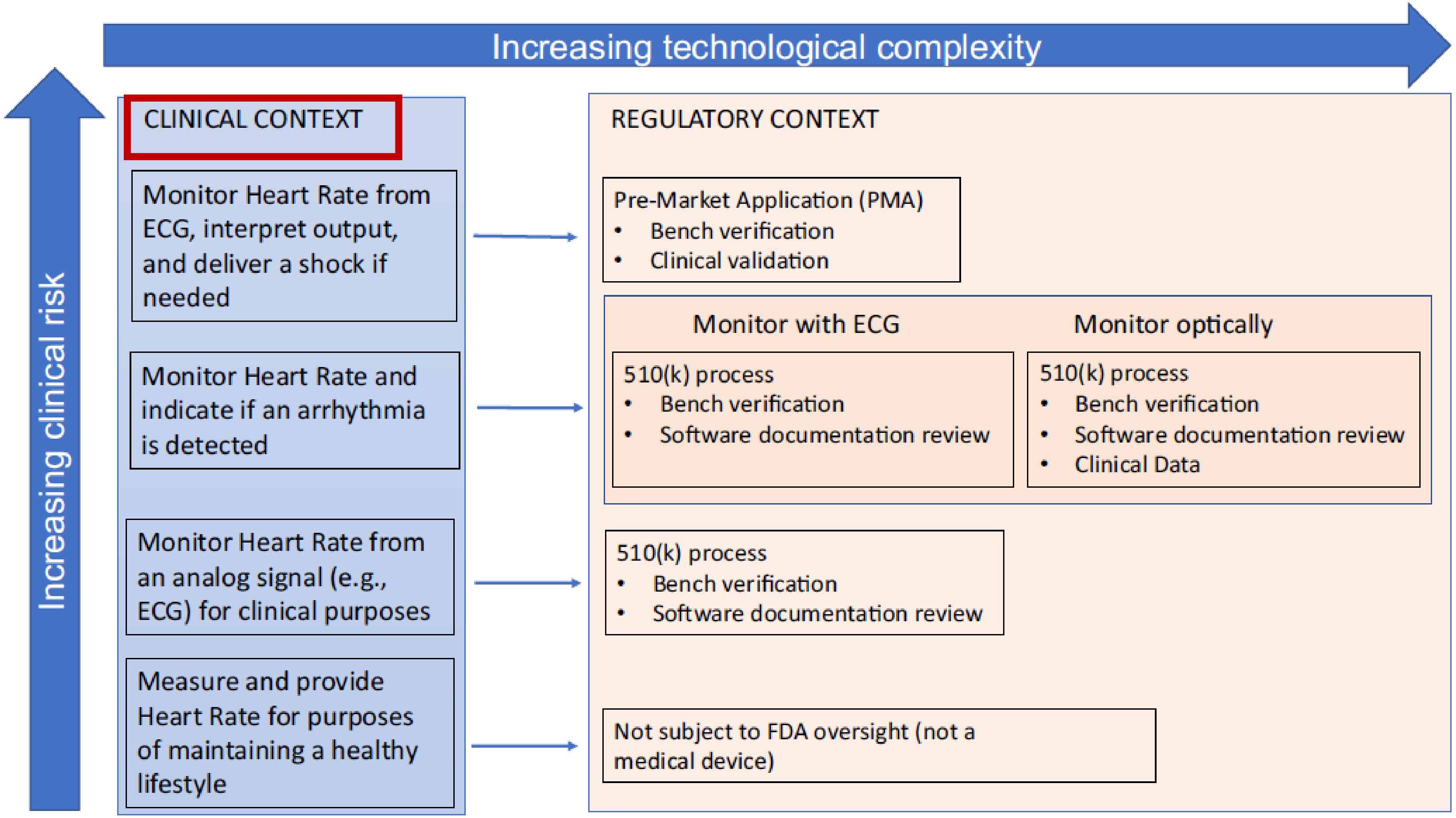
	Treat or Diagnose	Drive Clinical Mgmt	Inform Clinical Mgmt
Critical	IV	III	II
Serious	III	II	I
Non-Serious	II	I	I

SaMD N12 Risk Categorization Framework



Software as a Medical Device (SaMD): Clinical Evaluation. IMDRF Final Document, 2017

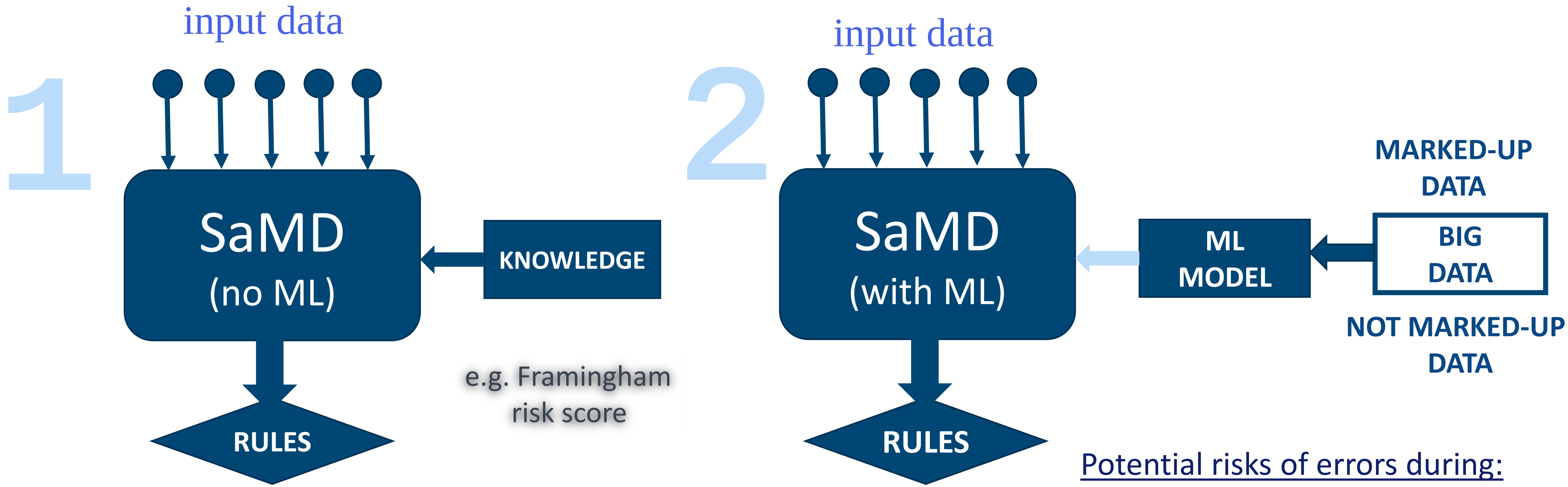
HEALTH RISKS from Medical Devices



Regulatory–Clinical–Technology risk paradigm. Examples of increasingly complex clinical applications of technology and their corresponding regulatory contexts are presented in this figure

S.C. Mathews et al. Digital health: a path to validation. Digital Medicine (2019) 2:38

TYPES OF CLINICAL DECISION SUPPORT SYSTEMS



<u>Potential risks of errors during:</u>

- obtaining medical data
- medical data processing
- model training

Clinical Validation Approaches Based on Analysis Tasks

diagnostic model

prediction model

event happened

event may happen

Testing Data

- reference data
- assessment at the current diagnostic process

- prospective data
- testing dataset

Dimopoulos et al. BMC Medical Research Methodology (2018) 18:179
https://doi.org/10.1186/s12874-018-0644-1

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

CrossMark

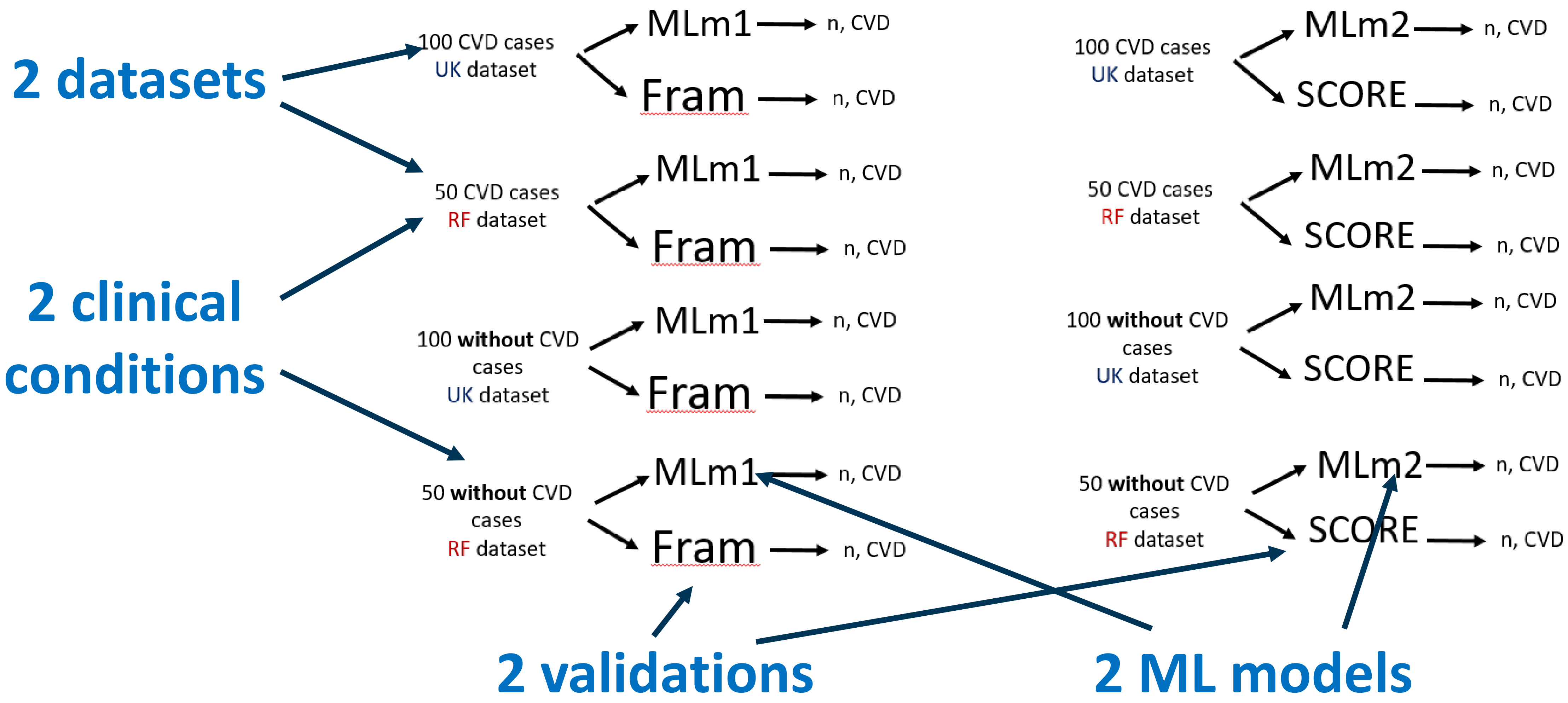
Machine learning methodologies versus cardiovascular risk scores, in predicting disease risk

Alexandros C. Dimopoulos[1,2], Mara Nikolaidou[2], Francisco Félix Caballero[3,4], Worrawat Engchuan[6], Albert Sanchez-Niubo[7,12], Holger Arndt[8], José Luis Ayuso-Mateos[3,5], Josep Maria Haro[4,7], Somnath Chatterji[9], Ekavi N. Georgousopoulou[1,10], Christos Pitsavos[11] and Demosthenes B. Panagiotakos[1,10*]

"The results showed that ML performs comparable well with the established risk tools in identifying a potential candidate for CVD development. In particular, three machine-learning classifiers were compared against an estimation tool for CVD risk prediction, as well as against actual CVD incidence, giving very high accuracy, sensitivity, and PPV for the classification…"

OUR EXPERIENCE WITH CLINICAL ML MODEL DESIGN

Clinical trial design for ML models

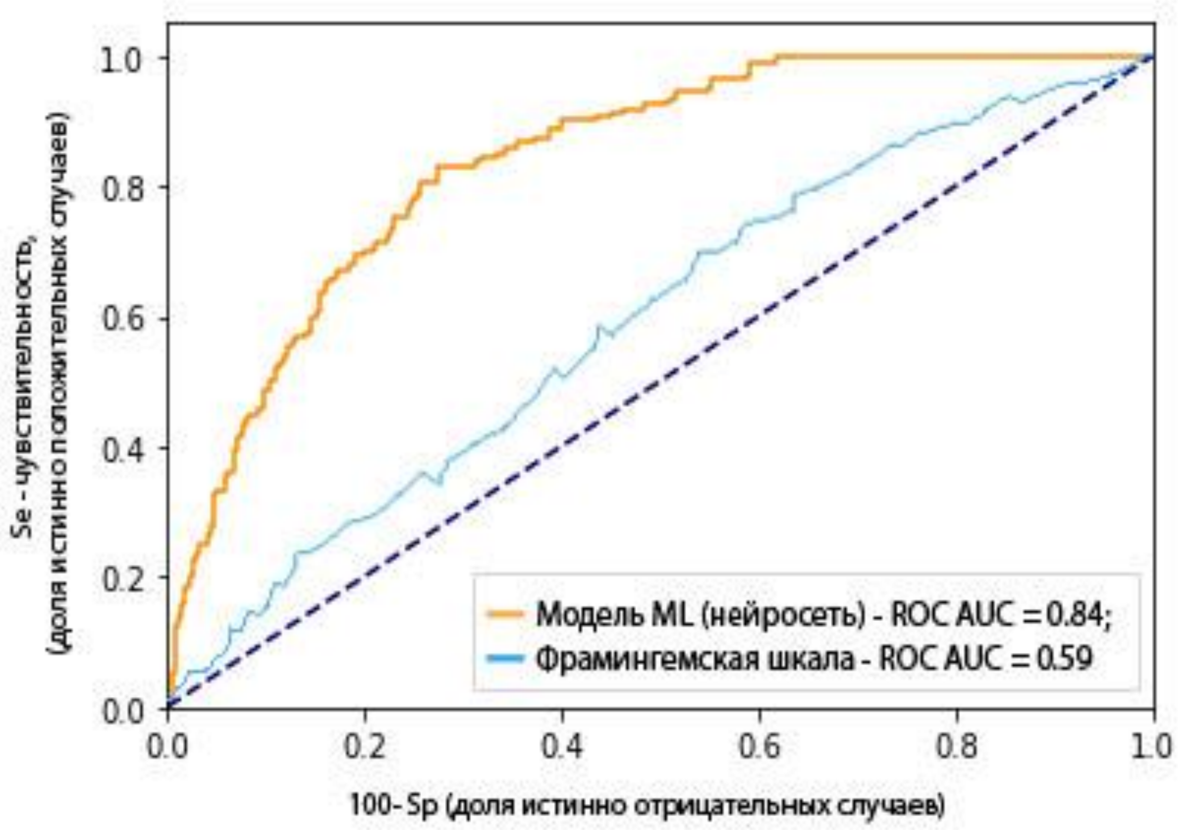


MATHEMATICAL CALCULATIONS TO DETERMINE THE ML MODELS ACCURACY

1 **building a classification with 4 situations:**
TP - true-positive,
FP - false-positive
TN - true-negative
FN - false-negative

2 **Se=TP/(TP+FN) – sensitivity**
Spe=TN/(TN+FP) – specificity

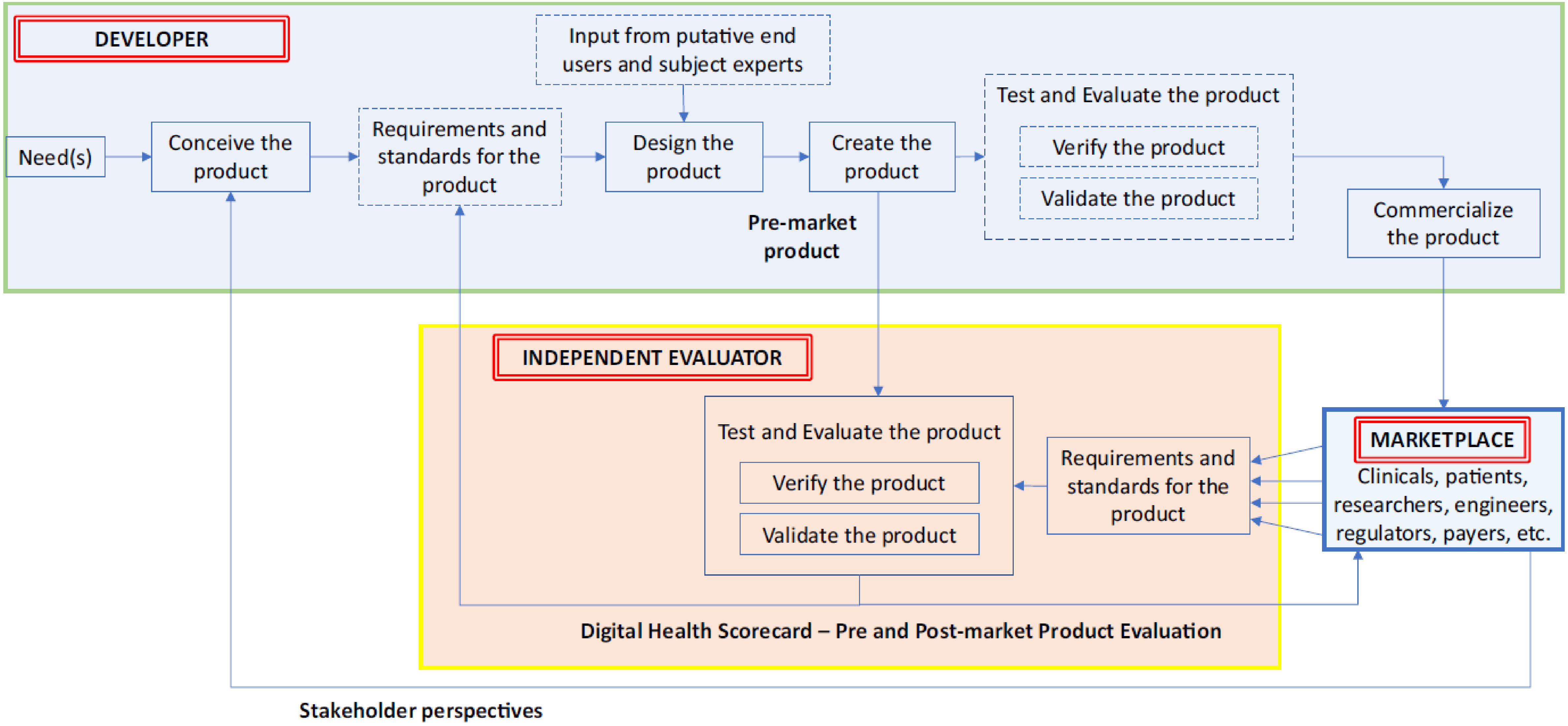
3 **Accuracy=(TP+TN)/(TP+FP+FN+TN)**
Roc-curves



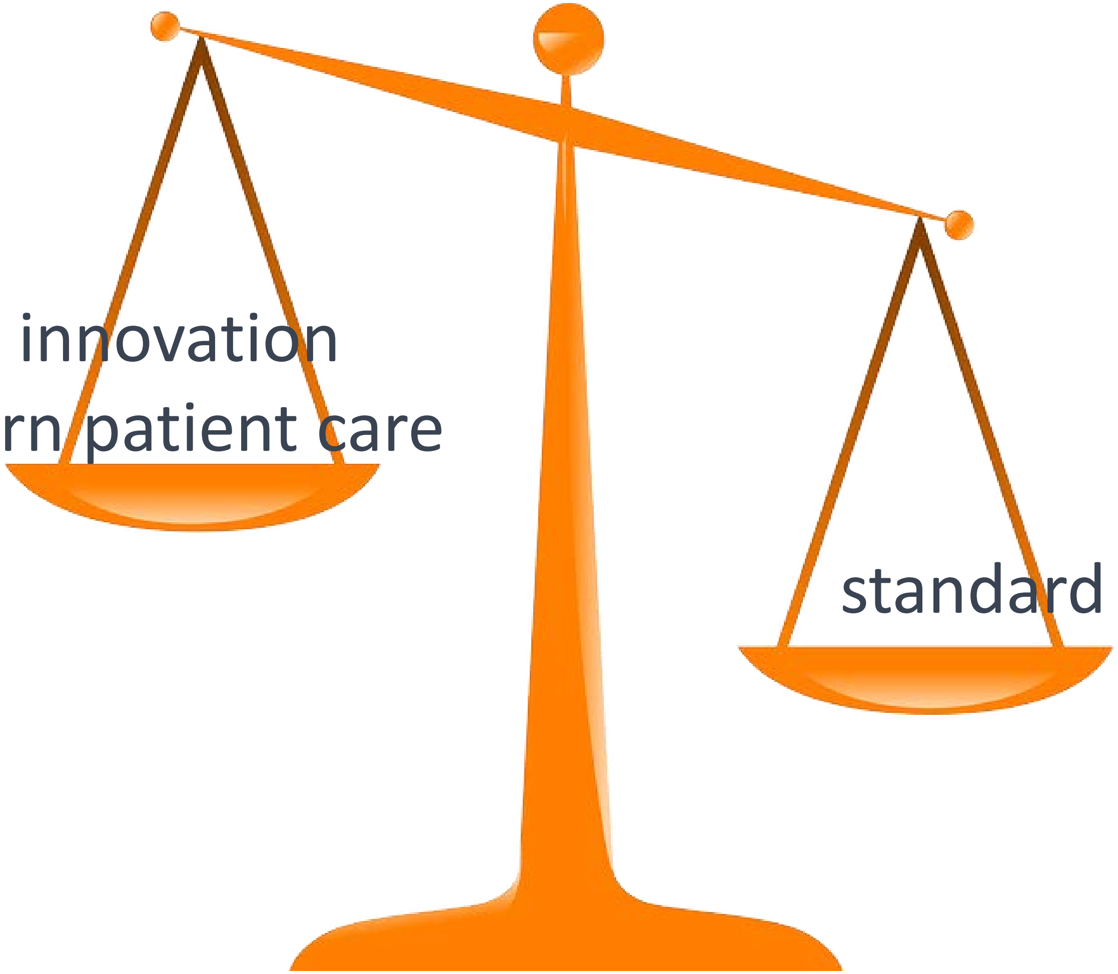
Roc-curves for the simulation results obtained for the Framingham scale and a ML model (neural network)

COLLABORATION WITH 2 NATIONAL CARDIOLOGY CENTERS FOR CLINICAL STUDIES OF MACHINE LEARNING MODELS

- The centers have departments of clinical research and trained specialists.
- There is an understanding of the need for a clinical trial Artificial Intelligence-based Clinical Decision Support System
- The clinical trial discussion process currently takes 2-3 months
- Moscow national cardiology center has a waiting list for clinical trials up to half a year
- National cardiology centers have their own data that can be used for clinical research. But is it necessary to audit this data for suitability for clinical research AI?



S.C. Mathews et al. Digital health: a path to validation. Digital Medicine (2019) 2:38


keep pace with innovation
promote modern patient care
standard for safety and effectiveness

CONCLUSIONS

- In Cardiology rapidly developing problem solving by using machine learning
- Examples of software implementation using machine learning models so far answer “simple” clinical questions
- The clinical context of the risk group and the ability of the model to predict the future are important in addressing the issue of clinical validation
- The Importance: readiness of research centers and clinical trials and duration of MD Model Software

Thanks for your attention!