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...

Karelian Republic

We are here now!

ML Specialists

Cardiologists

IT Specialists
Challenges of Applying ML in Healthcare

- quality data sets
- evidence of clinical efficacy and safety of machine learning software
• Artificial intelligence in cardiology
• The need for clinical trials of artificial intelligence
• Clinical trial problems
• Our experience
• Conclusions
BREAKING NEWS ABOUT ARTIFICIAL INTELLIGENCE IN HEALTHCARE IS BECOMING THE NORM OF OUR LIFE

ORIGINAL RESEARCH ARTICLE

Machine Learning to Predict the Likelihood of Acute Myocardial Infarction

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 [MI²]) 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. MI² 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 by calibration and c-index under the receiver operating characteristic curve.

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
<table>
<thead>
<tr>
<th>Topic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Text Speech Recognition</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Predictions CVD, IM</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Methodology ML</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
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)
"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
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 an 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

<table>
<thead>
<tr>
<th>SaMD Categories</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 N12 Risk Categorization Framework

Software as a Medical Device (SaMD): Clinical Evaluation. IMDRF Final Document, 2017
Regulatory–Clinical–Technology risk paradigm. Examples of increasingly complex clinical applications of technology and their corresponding regulatory contexts are presented in this figure.
TYPES OF CLINICAL DECISION SUPPORT SYSTEMS

1. **SaMD (no ML)**
   - Input data
   - Knowledge
   - Rules
   - Example: Framingham risk score

2. **SaMD (with ML)**
   - Input data
   - ML model
   - Big data
   - Not marked-up data

Potential risks of errors during:
- obtaining medical data
- medical data processing
- model training
Clinical Validation Approaches Based on Analysis Tasks

- diagnostic model
  - event happened
  - reference data
  - assessment at the current diagnostic process

- prediction model
  - event may happen
  - prospective data
  - testing dataset

Testing Data
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

2 datasets
- 100 CVD cases UK dataset
- 50 CVD cases RF dataset
- 100 without CVD cases UK dataset
- 50 without CVD cases RF dataset

2 clinical conditions
- MLm1 → n, CVD
- Fram → n, CVD
- MLm1 → n, CVD
- Fram → n, CVD
- MLm1 → n, CVD
- Fram → n, CVD
- MLm1 → n, CVD
- Fram → n, CVD
- MLm2 → n, CVD
- SCORE → n, CVD
- MLm2 → n, CVD
- SCORE → n, CVD
- MLm2 → n, CVD
- SCORE → n, CVD
- MLm2 → n, CVD
- SCORE → n, CVD

2 validations

2 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. \[ Se = \frac{TP}{TP+FN} \] – sensitivity
   \[ Spe = \frac{TN}{TN+FP} \] – specificity

3. Accuracy = \[ \frac{(TP+TN)}{(TP+FP+FN+TN)} \]

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?
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!