Identifying and Controlling Variability in Digital Health Measures in Parkinson's disease Clinical Trials

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Objective:

The 3DT initiative of the Critical Path for Parkinson's Consortium (CPP) aims to advance the regulatory maturity of digital biomarkers, for clinical studies in Parkinson's. This presentation highlights the progress of a Working Group established to identify sources of variability (SoVs) introduced by the implementation of digital measurements.

Background:

Efforts to create robust and generalisable digital endpoints for clinical trials are still ongoing. Digital endpoints are affected by SoVs associated with the device used, environmental factors, and quality of information. Robust digital endpoints need to have these SoVs addressed before they can be confidently incorporated in clinical trial protocols.

Methods:

Drawing from the research literature, an inventory of SoVs was developed with reference to three specific areas of concern, i.e., device, environment, and quality of information. Further, using information from WATCH-PD, an observational cohort study, and supplementary data contributed by WG participants, a data-driven approach was adopted to conduct an in-depth investigation of the SoVs and suggest effective mitigation strategies.

Results. Four factors were explored in-depth that related to the core sources of measurement SoVs namely, orientation and on-body sensor placement; the number of sensors and sampling rate; environmental factors relating to the subject home setting; and algorithm selection for classification employed for the prediction of clinical rating scales.

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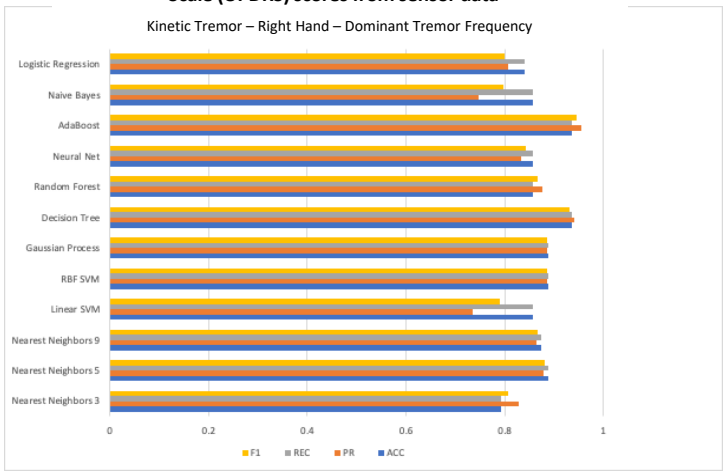
Furthermore, we have developed a structured approach to investigating the potential implications of different SoVs in the context of a particular clinical study around three principles:

Principle 1: Establish the suitability and characteristics of an Active vs Passive Measurement Protocol

Principle 2: Identify SoVs Associated with each of the Acquisition, Management, and Analysis stages of the Measurement Protocol

Principle 3: Adopt a risk management approach to characterise SoVs in terms of low-, medium- and high-impact

Figure 1. Exploring SoVs due to algorithm selection used to infer Unified Parkinson's Disease Rating Scale (UPDRS) scores from sensor data



Performance Metrics: F1: F-1 Score; REC: Recall; PR: Precision; ACC: Accuracy
Method Legend: SVM: Support Vector Machine; RBF: Radial Basis Function; K-Nearest Neighbour Methods using 3, 5 and 9; All methods implemented using SciKit Learn in python

Conclusions:

Clinical study protocols can effectively control SoVs affecting the reliability and reproducibility of digital biomarkers, through careful determination of data collection methods and requirements. In particular, quantitative analysis of the effect of key SoVs can determine their implications on recruitment requirements and statistical power calculations.

Figure 2. Mapping SoVs across different measurement protocol phases

Protocol Stage	SoV
Data acquisition	Device/sensor configuration Assessment tasks and duration Sensor positioning and orientation Environment Schedule of assessment Precision and frequency
Data management	Source data file transmission Data receipt notification Data quality control (missing data, malfunctioning device or sensor, erroneous sampling, erroneous transmission, corrupted storage, timing errors) Adverse events assessment Notification of data quality concerns and troubleshooting
Data analysis	Signal processing method used for feature extraction Signal processing architecture: edge, cloud or hierarchical/hybrid Documentation of algorithms and implementation

Next Steps:

The 3DT SoV Working Group is currently developing these ideas into a full report demonstrating the application of the structured approach developed in the context of specific case studies. This report, incorporating lessons, case studies and a discussion of practical implications will be released in 2021 as an open access publication.

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