**PROBAST**

Study:

An Individualized Multi-Modal Approach for Detection ofMedication “Off” Episodes in Parkinson’s Disease viaWearable Sensors

Step 2: Type of prediction study

**Is the study a diagnostic or a prognostic study?**

Diagnostic

**Is the study a development only, development and validation or validation only study?**

Development only

**What is the model of interest?**

Canonical correlation analysis

**What is the outcome of interest?**

Distinguishing patient PD on and off states

Step 3: Assess risk of bias

**Domain 1: Participants**

**Describe the sources of data and criteria for participant selection**

We recruited 25 patients diagnosed with PD by certified movement disorder specialists according to the United Kingdom Parkinson’s Disease Society Brain Bank Criteria.Exclusion criteria included (i) atypical Parkinsonism, (ii) depressive mood identified byBeck Depression Inventory-II (BDI-II)>14 or concurrent treatment with antidepressants,(iii) cognitive impairment measured by Montreal Cognitive Assessment ≤22, (iv) history of epilepsy, polyneuropathy, spinal cord diseases, thyroid dysfunction, or severe dermatological conditions, and (v) history of deep brain stimulation, implantation of any medical devices, or anticholinergic medication use.

**1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?**

Y

**1.2 Were all inclusions and exclusions of participants appropriate?**

PY

**Risk of bias introduced by selection of participants:**

Low

**Rationale of bias rating**

Reasonable exclusion criteria for PD

**Domain 2: Predictors**

**List and describe predictors included in the final model, e.g. definition and timing of assessment**

A wearable wristband, E4 wristband® (Empatica Inc., Milan, Italy), was used toobtain EDA, HR, BVP, and TEMP information.

**2.1 Were predictors defined and assessed in a similar way for all participants?**

Y

**2.2 Were predictor assessments made without knowledge of outcome data?**

Y

**2.3 Are all predictors available at the time the model intended to be used?**

Y

**Risk of bias introduced by predictors or their assessment**

Low

**Rationale of bias rating**

Independent and applicable predictors

**Domain 3: Outcome**

**Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination:**

An activity log was kept by the patients that contained their self-reports of time past from the latest dose, sleep, and ON/OFF reports performed every 30 minutes while wearing the device for a period of 24 hours. A report of “OFF” from any patient meant that he/she felt the urge for the medication, and “ON” had the opposite interpretation.

**3.1 Was the outcome determined appropriately?**

Y

**3.2 Was a pre-specified or standard outcome definition used?**

Y

**3.3 Were predictors excluded from the outcome definition?**

Y

**3.4 Was the outcome defined and determined in a similar way for all participants?**

Y

**3.5 Was the outcome determined without knowledge of predictor information?**

PN

**3.6 Was the time interval between predictor assessment and outcome determination appropriate?**

Y

**Risk of bias introduced by the outcome or its determination**

Low

**Rationale of bias rating**

Patient reported outcomes good standard outcome for PD medication assessment. However, there may be the chance that patients used activity data in their decision making for On and off state.

**Domain 4: Analysis**

**Describe number of participants, number of candidate predictors, outcome events and events per candidate predictor**

25 patients recruited. For this proof-of-principle study, we restricted ourselves to the12 subjects who documented “OFF” states in their diary. The other 13 subjects declaredthey had WO episodes but had failed to record this in their diary.

**Describe how the model was developed, predictor selection and risk group definition**

Preprocessing and feature extraction of raw time wearable data with empirical mode decomposition

**Describe whether and how the model was validated, either internally (cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants)**

No cross-validation: The CCA algorithm was trained on 65% of the data (randomly chosen) and validated on the remaining 35%.

**Describe the performance measures of the model, e.g. calibration, discrimination, classification, net benefit, and whether they were adjusted for optimism**

Pearson correlation coefficient

**Describe any participants who were excluded from the analysis**

Not described

**Describe missing data on predictors and outcomes as well as methods used for missing data**

For this proof-of-principle study, we restricted ourselves to the12 subjects who documented “OFF” states in their diary. The other 13 subjects declaredthey had WO episodes but had failed to record this in their diary.

**4.1 Were there a reasonable number of participants with the outcome?**

N

**4.2 Were continuous and categorical predictors handled appropriately?**

Y

**4.3 Were all enrolled participants included in the analysis?**

N

**4.4 Were participants with missing data handled appropriately?**

PY

**4.5 Was selection of predictors based on univariable analysis avoided?**

Y

**4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls)**

**accounted for appropriately?**

Y

**4.7 Were relevant model performance measures evaluated appropriately?**

N

**4.8 Were model overfitting and optimism in model performance accounted for?**

N

**4.9 Do predictors and their assigned weights in the final model correspond to the results**

**from multivariable analysis?**

Y

**Risk of bias introduced by the analysis**

High

**Rationale of bias rating**

Small amount of patients, more than half of patients were excluded due to no off state. Only correlation coefficient reported, no classification metric.

**Overall Risk of bias**

High