ai·prognosis

D5.1 / Study initiation package (dBM-DEV study)

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Document history

Version	Date	Contributors	Action / status
0.1	20/05/2024	TUD, AUTH	Document structure (table of contents) ready
0.2	29/05/2024	TUD	First draft
0.3	30/05/2024	TUD	Minor changes
0.4	05/06/2024	TUD	Added dates for protocol submission and approval for FIN; ready for quality check
0.5	09/06/2024	AUTH, TUD	Document revised after quality check
0.6	20/06/2024	TUD	Additional edits after quality check
0.7	20/06/2024	CHUT, AUTH	Additional edits after quality check
0.8	26/6/2024	TUD, AUTH	Minor edits; Ready for internal review
0.8	12/07/2024	CING	Reviewed by Paraskevi Chairta (CING) Kyproula Christodoulou (CING)
0.8	11/07/2024	DBC	Reviewed by Sotirios Michagiannis (DBC)
0.9	15/07/2024	TUD, AUTH	Minor edits; submitted for approval by Project Coordinator; Approved for submission by the Project Coordinator
1.0	16/07/2024	AUTH	Submitted version

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List of abbreviations

CDM	Clinical data management
dBM	Digital biomarker
dBM-DEV	The Digital Biomarkers development, validation and verification study
eCRF	Electronic case report form
EDC	Electronic Data Capture
ESS	Epworth Sleepiness Scale
HTTP	Hypertext transfer protocol
HTTPs	Hypertext transfer protocol secure
ICF	Informed consent form
ICSD-3	International Classification of Sleep Disorders, 3rd Edition
IRB	Institutional Review Board (or Ethics Committee)
MDR	Medicinal Device Regulation
MDS-UPDRS	Movement Disorders Society - Unified Parkinson Disease Scale
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
PDQ-8	Parkinson's disease questionnaire, 8-item version
RBD	REM sleep behaviour disorder
RBDSQ	REM sleep behaviour disorder screening questionnaire
REM	Rapid eye movements
SSL/TLS	Secure Sockets Layer/Transport Layer Security
URL	Uniform Resource Locator
VCPU	Virtual Central Processing Unit
VM	Virtual Machine

Executive summary

The Digital Biomarkers development, validation and verification (dBM-DEV) study is a multicentre observational clinical study. The ultimate aim of the dBM-DEV study is to develop and validate smartwatch-based digital biomarkers (dBM) for REM sleep behaviour disorder (RBD) and day-time somnolence, as well as to verify existing smartwatch and smartphone-based dBMs that assess motor and cognitive function. The dBM-DEV study was written collaboratively and submitted for review to the respective local ethical committees at all study sites [Technische Universität Dresden (TUD), Centre Hospitalier Universitaire de Toulouse (CHUT), Fundacion Iniciative para las Neurociencias (FIN), King's College London (KCL)]. This report outlines the actions required for the study protocol preparation, approval, organisation and data collection process of the study. Study documents were appropriately submitted to local ethics committees at the four clinical centres. Protocol revisions were made based on consortium discussions and agreements and multicentre institutional review board (IRB) feedback. In the same vein, each site prepared the associated documents, such as the informed consent forms (ICF) to ensure compliance with the regulatory rules. The study was registered on clinicaltrials.gov (NCT06444789). The OpenClinica platform was set up and electronic case report forms (eCRFs) were created to serve the needs of clinical assessment data logging. Multiple user roles and permissions were defined to ensure user access control, as well as data quality and integrity. The approved study protocol, the ICFs, the study approval letters from the three IRBs (TUD, CHUT, FIN) and a snapshot of the listing of the study in clinicaltrials.gov.

1 Introduction

1.1 Document scope

D5.1 is the initiation package of the dBM-DEV study. The dBM-DEV study is the first clinical study of the AI-PROGNOSIS project, conducted by four study sites [Technische Universität Dresden (TUD), Centre Hospitalier Universitaire de Toulouse (CHUT), Fundacion Iniciative para las Neurociencias (FIN), King's College London (KCL)]. It aims to identify novel digital biomarkers for the detection of REM Sleep Behaviour Disorders (RBD) and daytime somnolence via a home-based assessment as its primary outcome. As secondary objectives, this study aims to validate already existing digital BioMarkers (dBMs) for motor and cognitive symptoms.

The scope of this deliverable is to ensure study initiation is on track. The study initiation package includes the documents necessary for the enrolment of the first study participant, i.e. the study protocol, the information sheets for the study participants, and the informed consent form (ICF). Furthermore, it includes the clinical study registration number in a registry meeting WHO criteria, in this case clinicaltrials.gov (NCT06444789). Writing the study protocol included establishing the functioning of the study teams and details of the study procedures. The procedures pertaining to study preparation, study registration and data management are outlined in this document. The latest version of the approved study protocol, the English version of the ICF, the study approval letters from three IRBs (pending approval at KCL), and a snapshot of the listing of the study at clinicaltrials.gov are included as appendices.

D5.1 reflects the progress of tasks T5.1 - Clinical study and eCRF management system and T5.2 Digital biomarkers development, validation and verification (dBM-DEV) study of the AI-PROGNOSIS project.

1.2 Document structure

The document includes five sections, and it is structured as follows:

- Section 1 provides a brief introduction to the present document.
- Section 2 describes the preparation process of the study protocol and consent form.
- Section 3 presents the study registration on clinicaltrials.gov.
- Section 4 presents the status of the IRB submissions to the local ethical committees.
- Section 5 describes the clinical data management.

In addition, the following documents are collated as appendices:

- The approved study protocol (latest version 1.1),
- The participant information sheet and consent form (English version),
- The study approval letters from three IRBs (TUD, CHUT, FIN), and
- A snapshot of the listing of the study in clinicaltrials.gov.

2 Study preparation

2.1 Summary of the research

The latest version (version 1.1) of the approved, full study protocol in English, is collated as an Appendix to this report. Here, a summary of the study is provided. The dBM-DEV study is

a multi-centre, observational study that will be conducted in Germany, France, Spain (FIN), and the United Kingdom (UK) by clinical partners (clinical sites) (TUD, study lead), CHUT, FIN, and KCL, respectively. The study will make use of a study app, digital active tests, and a smartwatch to develop and verify digital biomarkers of Parkinson's disease (PD) symptoms and medication side effects.

The main objective of the dBM-DEV study is to identify a novel, robust dBM for the detection of REM sleep behaviour disorder (RBD) using passively-captured accelerometer and heart activity data from a smartwatch. Specifically, the project aims to identify features extracted from passive smartwatch data collection that are associated with episodes of RBD and to demonstrate that these features can potentially help increase specificity of RBD detection as compared to the score of the RBD screening questionnaire (RBDSQ), which is 0.56, indicating that 44% of patients screened with the RBDSQ will be false-positive (positive screening result, but no RBD, Stiasny-Kolster et al., 2007).

Secondary objectives aim to identify mobility patterns (features) that correlate with the extent of daytime somnolence as reported by the score of the Epworth Sleepiness Scale (ESS), and to verify feasibility to acquire dBMs of motor symptoms (tremor, bradykinesia, dyskinesias, gait, and posture) and non-motor symptoms (cognitive deficit). Performance of dBMs will be evaluated, correcting for age and sex. Information of the racial group of participants will be collected to evaluate the diversity of the cohorts, but not corrected for since the sample is small. Furthermore, information of the type of settlement of participants (city, large town, small town, village) will be recorded to potentially identify or even correct for different movement patterns. Further details can be found in the complete study protocol attached as an appendix to this report.

The dBM-DEV sub-study is conducted stepwise on two subsequent cohorts referred to as the development cohort (comprising 30 patients with RBD and 30 matched controls) and the confirmation cohort (comprising 30 patients with PD). Following a baseline visit, participants will undergo daily-life dBM tracking over a duration of four weeks (development cohort) and three months (confirmation cohort), respectively. Additionally, PD patients enrolled in the confirmation cohort will undergo a polysomnography session.

For both cohorts, participants will be recruited from the movement disorders outpatient clinics of the neurology department of each of the four clinical sites participating in the study. Healthy participants will be recruited by outreach activities that include conventional media (like newspapers) and social media. Recruiting material will be provided to the Ethics committees as it becomes available. RBD only affects 0.5%-1% of the general population. To ensure a sufficiently high number of participants with RBD in the development cohort, we will mainly draw on the existing cohorts of RBD patients in each study site. **Table 1** gives a summary of the research elements of the study protocol.

Table 1 Summary of the dBM-DEV study

Title	AI-PROGNOSIS: Digital biomarkers development, validation and verification substudy (dBM-DEV study)
JUSTIFICATION/ CONTEXT	REM sleep behaviour disorder (RBD) is the best predictor for neurodegenerative diseases with synuclein pathology, including Parkinson's disease (PD). Yet, RBD only affects 0.5-1 % of the general population. It can only be confirmed by polysomnography, which is a cumbersome procedure that cannot be used for screening. A RBD screening questionnaire (RBDSQ) has been developed which has high sensitivity but low specificity.

Primary Objective	The main objective of this study is to identify a novel, robust dBM for the detection of RBD using smartwatch-based recordings of passive data. Specifically, this study aims to identify features extracted from passive smartwatch data that are associated with episodes of RBD and demonstrate that these features can potentially help increase **specificity** of RBD detection as compared to the score of the RBD screening questionnaire (RBDSQ).
Secondary Objectives	1. demonstrate that **sensitivity** of RBD detection can be improved via dBM measurements as compared to the score of the RBD screening questionnaire. 2. identify mobility patterns (features) that correlate with the extent of daytime somnolence as reported by the score of the Epworth Sleepiness Scale (ESS). 3. verify feasibility to acquire dBM for motor symptoms (bradykinesia, tremor and dyskinesias, gait, posture) and non-motor symptoms (cognition) 4. evaluate the performance of the dBMs correcting for age and sex.
Outline of the research	This is a multicentre observational research study. The study is conducted step-wise on two subsequent cohorts referred to as the development cohort (comprising 30 patients with RBD and 30 matched controls) and the confirmation cohort (comprising 30 patients with PD). Following a baseline visit, participants will undergo daily-life dBM tracking over a duration of 4 weeks and 3 months, respectively. Additionally, PD patients enrolled in the confirmation cohort will receive a polysomnography. The investigation is conducted in four European sites. Each site will submit this protocol to their local ethics committee.
Inclusion Criteria	**<u>Participants of the "Development cohort":</u>** **RBD patients:** • Age: >18 years • Written declaration of informed consent • The participant is using a compatible smartphone, a smartwatch will be provided for the duration of the study • The participant has a care partner with whom they share their bedroom at night • Known RBD as defined by the International Classification of Sleep Disorders (ICSD-3) as demonstrated by polysomnography with at least one episode of RBD per week (on average over the last month, frequency reported with the help of the care partner). **Healthy matched controls:** • Healthy volunteers demographically matched to the enrolled RBD patients. • Written declaration of informed consent • The participant is using a compatible smartphone; a smartwatch will be provided for the duration of the study. • No history of RBD.

	<u>Participants of the "Confirmation cohort":</u> • Age: >18 years. • Diagnosis of PD • RBDSQ score 3 - 12 points • Absence of dementia • Written informed consent • The participant is using a compatible smartphone, a smartwatch will be provided for the duration of the study • Participants have a care partner.
Exclusion criteria	• Inability to consent for study procedures as judged by the investigator. • Lacking motivation to participate in study procedures as judged by the investigator. • Lack of social security.
Main Evaluation Criterion	As the primary outcome measure, we will determine the number of nights with dBM features reported by the smartwatch that in the development cohort correlated with the occurrence of RBD episodes. The study will be considered positive if RBD-associated features are not observed in at least 40% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD as confirmed by polysomnography.
Secondary Evaluation Criteria	• Spearman correlation coefficient between smartwatch-based features and the Epworth Sleepiness Scale (ESS) • continuity of motion tracking for analysis of motor dBM • number and quality of acquired videos for analysis of gait and posture • number of completed cognitive tasks • Correlation coefficients corrected for age and sex
Study size	A total of 90 participants will be enrolled in the study across the two subsequent cohorts, including 30 RBD patients and matched 30 controls in the "development cohort" and 30 patients with PD in the "confirmation cohort".
Duration of the research	**Development cohort:** - Duration of the recruitment period: 6 months - Follow-up period per participant: 4 weeks - Total research duration: 7 months **Confirmation cohort:** - Duration of the recruitment period: 6 months - Follow-up period per participant: 3 months - Total research duration: 9 months
EXPECTED BENEFITS	It is hoped that the identification of robust dBMs in this study will have a favourable impact on the PD community in the future by enabling the daily-life detection and monitoring of PD symptoms, including the early signs of the disease such as RBD.

2.2 Study protocol preparation

2.2.1 First draft of the study protocol

The first draft of the study protocol was written by TUD and completed on 10/09/2023. It was circulated among the rest of the clinical partners (CHUT, FIN, CKL) and the technical partners [Katholieke Universiteit Leuven (KUL), Centre for Research and Technology Hellas (CERTH), Aristotle University of Thessaloniki (AUTH), SquareDev (SQD), Netcompany-Intrasoft (INTRA)] involved in the study. The study protocol (version 1.0) was finalised on 27/11/2023. Subsequently, the protocol document was adjusted by each clinical partner to the requirements of their local ethical committees (also referred to as institutional review boards (IRBs)).

Writing the study protocol first included identifying the RBD detection via a home-based assessment as an unmet clinical need in PD care and thus entailed the abovementioned literature research. Furthermore, the clinical partners had to come to an agreement about the assessments necessary to reach the primary and secondary endpoints. This also made close cooperation with the technical partners of this project necessary to ensure accurate detection of dBMs and assess possibilities for technological advances and identify possible pitfalls of the study's design. This also meant for the clinical partners to agree on types of source data and on which clinical assessment data to enter into the clinical data management system (see Section 4). Guidelines for collecting and recording data in the clinical data management system were laid out. The clinical and technical partners also agreed on how to arrive at data clearance of both the clinical data recorded via the clinical management system and the dBM data.

2.2.2 Submission to ethical committees

Table 2 below shows the status of IRB submissions at all four study sites. All four clinical centres submitted the study documents to their respective local ethics committees, i.e.,

- Comité de protection des personnes Ile de France III (CHUT),
- Comité de Ética de la Investigación con medicamentos del Hospital Ruber Internacional de Madrid (FIN),
- Ethikkommission an der TU Dresden (TUD), and
- North of Scotland Research Ethics Committee 1 (KCL).

Submissions were accepted at TUD, CHUT and FIN; decision is still pending at KCL.

Table 2 Dates of IRB submissions, responses and approval.

Study site	First submission	First response	Approval
TUD	19/12/2023	11/03/2024	31/05/2024 (version 1.1)
CHUT	21/12/2023	23/01/2024	06/02/2024 (version 1.0)
KCL	10/05/2024	Not available	Pending (version 1.2)
FIN	10/03/2024	29/04/2024	06/05/2024 (version 1.1)

2.2.3 Protocol revisions

IRBs at FIN and CHUT had no comments that required changes to the protocol. The IRB at TUD was concerned whether the study was affected by the Medicinal Device Regulation (MDR). The clinical partners were able to clarify that the dBM-DEV study is a scientific study

that does not fall under the MDR. The IRB at TUD also had questions about statistical planning, which were addressed in a revised study protocol version (version 1.1).

To make sure all clinical centres are aligned with the same protocol version, amendments have been submitted or will be submitted by each centre to include TUD's revisions following their IRB's requirements. Further revisions currently under preparation to be notified to the local ethics committees by all centres include the following additions to the protocol:

- Collection of participants' racial group and settlement
- Collection of keystroke-related data during routine typing using a custom virtual keyboard for estimating bradykinesia-related dBMs.

Due to the sensitive nature of the underlying information, those aspects were left out of the first version of the protocol in order not to risk a rejection of the study that would cause a considerable delay. The amendments (protocol version 1.2) are expected to be submitted by early July 2024 in TUD, CHUT, and FIN IRBs. Due to local regulatory differences, version 1.2 of the protocol (including the aforementioned changes) was submitted to the IRB at KCL directly.

2.3 Informed consent forms preparation

Informed consent forms (ICF) were written by each study site independently based on existing templates in the local language that comply with local regulatory requirements. Translated forms were exchanged to ensure consistency of ICFs across sites. These forms are collated as appendices to this report.

3 Study registration

The study was submitted for registration on clinicaltrials.gov by CHUT on 14/05/2025. After revision, it was resubmitted and approved on 06/06/2024. The clinical study identifier is: NCT06444789[1].

4 Clinical data management

OpenClinica[2] 3.16 Community Edition will be employed for capturing and storing clinical assessment data. OpenClinica is an open-source Electronic Data Capture (EDC) and a Clinical Data Management (C) software published under the GNU Lesser General Public License as a free software. It will facilitate the management of the Electronic Case Report Forms (eCRF), the storage and export of the data captured.

An instance of the OpenClinica is hosted in the AI-PROGNOSIS Cloud infrastructure that is managed by INTRA in a Virtual Machine (VM) provided by the Hetzner Cloud provider. Hetzner data centres are certified in accordance with ISO/IEC 27001[3][4]. The OpenClinica instance is hosted in a VM with 2 VCPU(Intel), 4GB RAM and 40GB Disk Local in their European data centres in Nuremberg, Germany. Traffic to and from the VM is controlled by a firewall set up by INTRA to only allow hypertext transfer protocol (HTTP) / hypertext transfer

[1] dBM-DEV study on clinicaltrials.gov - https://classic.clinicaltrials.gov/ct2/show/NCT06444789
[2] OpenClinica Community Edition: https://www.openclinica.com/get-free-community-edition-software/
[3] Hetzner Data Centre: https://www.hetzner.com/unternehmen/rechenzentrum
[4] Hetzner security and data protection: https://www.hetzner.com/assets/Uploads/downloads/Sicherheit-en.pdf

protocol secure (HTTPs) traffic. The OpenClinica instance can be accessed by following the https://openclinica.ai-prognosis.eu/ URL.

The hosting environment in the VM is separated in three Docker containers. An NGINX container is managing the SSL/TLS encryption enabling the use of HTTPs, a container running a custom image based on Apache Tomcat 7.0 is running the main web application of the OpenClinica and a third container is running a Postgres 9.5 database which stores all the data generated by the OpenClinica. Hetzner native backup solution will be utilised as a backup strategy. A snapshot of the disk state is captured every day, and a history of 7 days is kept.

OpenClinica allows the creation of studies and the assignment of multiple sites below them. This effectively creates a separation layer between the sites, thus not allowing users from one site view or export data from the other. Users can be either normal users or technical/business administrators. User roles can be assigned either per study or per site, thus providing the appropriate access control between the sites. The user roles provided by the OpenClinica per study are 1) Study Director, 2) Data Manager, 3) Data Entry Person, 4) Data Specialist and 5) Monitor. In addition, the roles available per site are 1) Clinical Research Coordinator, 2) Investigator and 3) Monitor. For the purposes of the of the dBM-DEV study, the role of Study Director will be assigned to the principal investigator of the study (from TUD) enabling them to oversee and manage the multiple sites. In addition, for each site, the role of the Investigator, Clinical Site Coordinator and Monitor will be assigned as shown in **Table 3**. Their respective permissions are presented in the **Table 4**.

In addition to the roles presented, the technical system administrator (role undertaken by AUTH) can access all data from all participants of all studies, manage and create users, create import and export jobs and perform general maintenance of the server.

Table 3 OpenClinica user roles used in each dBM-DEV study site

User role	TUD	CHUT	FIN	KCL
Study director	1	-	-	-
Investigator	2	2	1	1
Clinical Site Coordinator	2	2	2	1
Monitor	1	1	1	1

Table 4 OpenClinica user role permissions

User role	Submit Data	Monitor and Manage Data	Extract Data	Study Setup
Study director	Add and Manage Subjects View, Schedule, and Enter Data into CRFs for Events No Waiting to Perform Double Data Entry After Initial Data Entry Import Data	Study Audit Log and Source Data Verification Create, Edit, and Manage CRFs	Yes (Study)	View and Build Study Assign Users

	Notes and Discrepancies			
Investigator	Add and Manage Subjects View, Schedule, and Enter Data into CRFs for Events Import Data Notes and Discrepancies	-	Yes (Site)	-
Clinical Site Coordinator	Add and Manage Subjects View, Schedule, and Enter Data into CRFs for Events Import Data Notes and Discrepancies	-	No	-
Monitor	View Subjects View Events Study Audit Log and Source Data Verification Notes and Discrepancies	Source Data Verification	Yes (Site)	-

The OpenClinica dashboard can be seen in **Figure 1**. Via the dashboard an overview of the general information for the enrolment, participant status, and events are presented. Two indicative eCRFs can be seen in **Figure 2**. Source Data Validation will be employed for the verification process of the eCRFs. After data entry persons mark the eCRFs complete the monitor will validate the source material, thus ensuring correct data was inputted in the database. In addition, the appropriate validation rules will be utilised in the eCRFs to prevent possible discrepancies in the data. For the purposes of the dBM-DEV study seven eCRFs were developed as shown in **Table 5**.

Table 5 eCRFs created for the dBM-DEV study

Name	**Description**
Inclusion/Exclusion	The inclusion/exclusion criteria of the dBM-DEV study.
Baseline Characteristics	Includes all the baseline characteristics of the participants based on their cohort such as demographics, PD related information, RBD related information.
Standardised scales and questionnaires	
MoCA	Montreal Cognitive Assessment (Nasreddine et al., 2005)
RBDSQ	REM Sleep Behaviour Disorder Screening Questionnaire (Stiasny-Kolster et al., 2007)
MDS-UPDRS	MDS-Unified Parkinson's Disease Rating Scale (Goetz et al., 2008)

PDQ-8	Parkinson's Disease Questionnaire-8 (Jenkinson et al., 1997)
ESS	Epworth Sleepiness Scale (Johns, 1991)

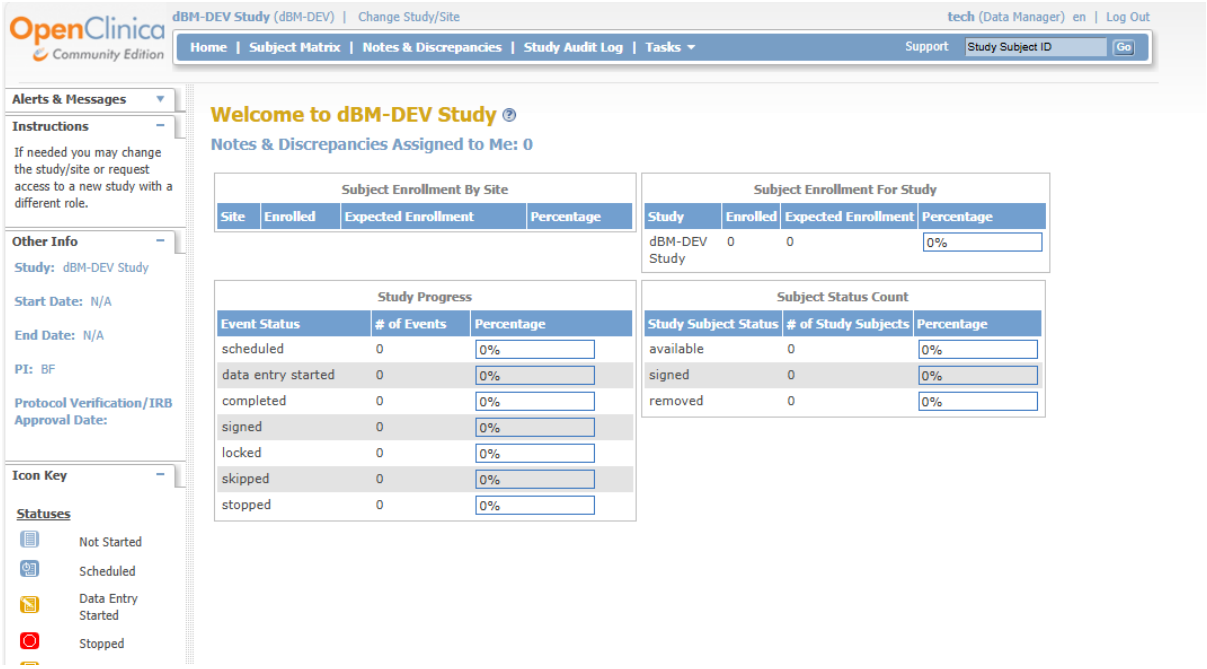

Figure 1 Screenshot of the OpenClinica dashboard

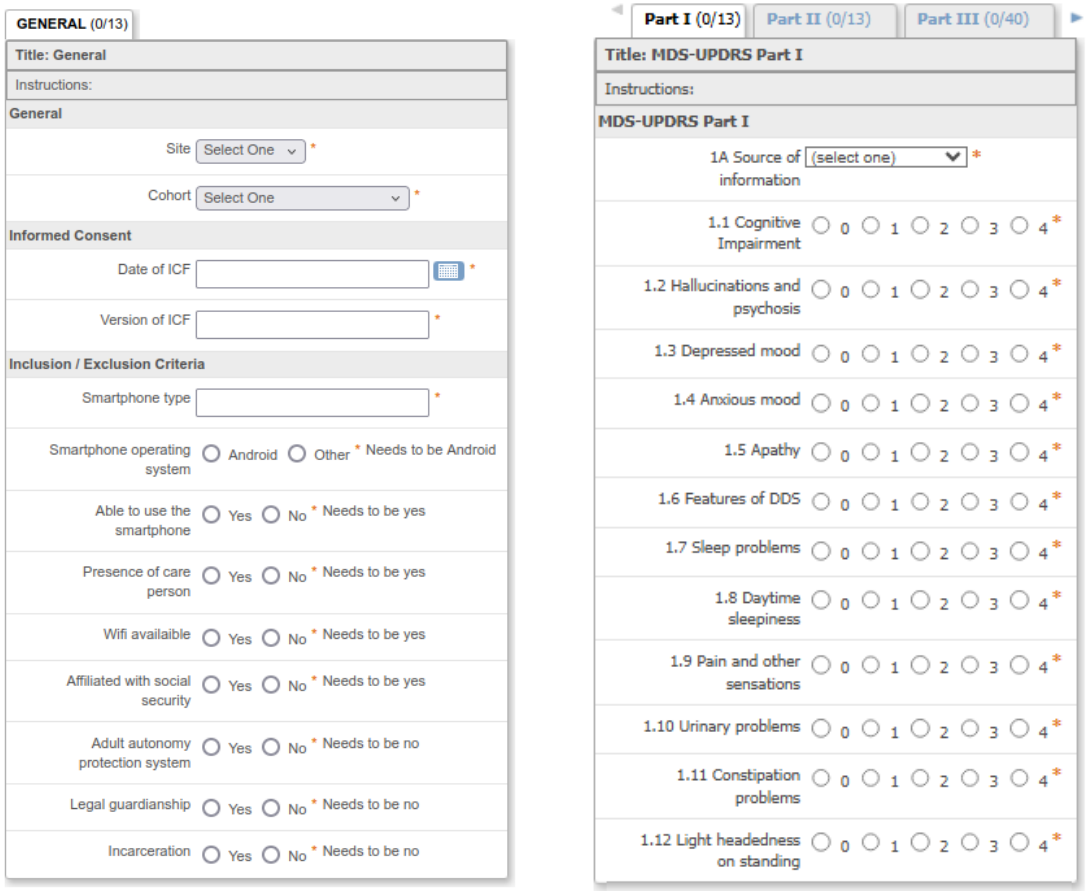

Figure 2 OpenClinica indicative eCRFs of the dBM-DEV study.

5 Conclusions

The key takeaways of D5.1 are:

- The dBM-DEV study is a multicentre observational clinical study aiming primarily to identify smartwatch-based digital biomarkers for the detection of RBD and of day-time somnolence.
- The study will establish the digital biomarkers for RBD and daytime somnolence in a development cohort and validate them in a confirmation cohort.
- The study will also verify the feasibility and performance of smartwatch- and smartwatch-based, passively captured digital biomarkers of resting tremor, bradykinesia, and dyskinesias and of active test-derived digital biomarkers of balance, posture, gait, and cognition.
- The study will be conducted in four countries, i.e., Germany, France, Spain, and the UK, by AI-PROGNOSIS clinical partners, TUD, CHUT, FIN, and KCL, respectively.
- Ethical approval was sought in all countries and obtained in Germany, France, and Spain; approval in the UK is pending.
- The study was registered in clinicatrials.gov (NCT06444789).
- The OpenClinica platform was set-up to serve the needs of clinical data logging and management; seven eCRFs were developed.

References

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., ... & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders: official journal of the Movement Disorder Society, 23*(15), 2129-2170.

Jenkinson, C., Fitzpatrick, R., Peto, V., Greenhall, R., & Hyman, N. (1997). The PDQ-8: development and validation of a short-form Parkinson's disease questionnaire. *Psychology and Health, 12*(6), 805-814.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep: Journal of Sleep Research & Sleep Medicine, 14*(6), 540–545.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699.

Stiasny-Kolster, K., Mayer, G., Schäfer, S., Möller, J. C., Heinzel-Gutenbrunner, M., & Oertel, W. H. (2007). The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. *Movement disorders, 22*(16), 2386-2393.

Appendix – Supplementary documents

The following documents are collated to this report.

S.1 Latest version of the approved study protocol (version 1.1)

S.2 English version of participant information sheet and consent form

S.3 Study approval letter (CHUT, France)

S.4 Study approval letter (FIN, Spain)

S.5 Study approval letter (TUD, Germany)

S.6 Snapshot of the listing of the study in clinicaltrials.gov

AI-PROGNOSIS: Digital biomarkers development substudy (dBM-DEV study)

Study protocol

Funded by the European Union

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HISTORY OF PROTOCOL UPDATES

Version	Author	Date	Reason for update
0.9	BF	27 NOV 2023	last common English version
1.0	BF	19 DEC 2023	submitted version
1.1	BF	18 APR 2024	• study title changed from “AI-prognosis digital biomarkers development study (dBM-DEV study)” to “AI-PROGNOSIS: Digital biomarkers development substudy (dBM-DEV study)” to reflect the fact that dBM-DEV is a substudy of the AI-PROGNOSIS study • clarification of the study purpose with respect to MDR as requested by TUD’s IRB • clarification of statistical planning as requested by TUD’s IRB, changed main outcome criterion 20% to 40% • ethnicity is recorded as required by the EU • question about RBD episode added to study protocol (previously in ICF)

PROTOCOL SIGNATURE PAGE

AI-PROGNOSIS: Digital biomarkers development substudy (dBM-DEV study)

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ai·prognosis

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List of abbreviations

CHUT	Centre Hospitalier Universitaire de Toulouse, France
dBM	Digital biomarker
ESS	Epworth Sleepiness Scale
FIN	Fundacion Iniciative para las Neurociencias, Spain
KCL	King's College London, UK
MDS-UPDRS	Movement Disorders Society - Unified Parkinson Disease Scale
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
PDQ-8	Parkinson's disease questionnaire, 8-item version
RBD	REM sleep behaviour disorder
RBDSQ	REM sleep behaviour disorder screening questionnaire
REM	Rapid eye movements
TUD	Technische Universität Dresden, Germany

1 Summary of the research

PERSON WHO DIRECTS AND SUPERVISES THE RESEARCH	Prof. Dr. med. Björn Falkenburger Klinik und Poliklinik für Neurologie Universitätsklinikum „Carl Gustav Carus“ Fetscherstraße 74 | 01307 Dresden
Title	AI-PROGNOSIS: Digital biomarkers development, validation and verification substudy (dBM-DEV study)
JUSTIFICATION/ CONTEXT	REM sleep behaviour disorder (RBD) is the best predictor for neurodegenerative diseases with synuclein pathology, including Parkinson's disease (PD). Yet, RBD only affects 0.5-1 % of the general population. It can only be confirmed by polysomnography, which is a cumbersome procedure that cannot be used for screening. A RBD screening questionnaire (RBDSQ) has been developed which has high sensitivity but low specificity.
Primary Objective	The main objective of this study is to identify a novel, robust dBM for the detection of RBD using smartwatch-based recordings of passive data. Specifically, this study aims to identify features extracted from passive smartwatch data that are associated with episodes of RBD and demonstrate that these features can potentially help increase **specificity** of RBD detection as compared to the score of the RBD screening questionnaire (RBDSQ).
Secondary Objectives	1. demonstrate that **sensitivity** of RBD detection can be improved via dBM measurements as compared to the score of the RBD screening questionnaire. 2. identify mobility patterns (features) that correlate with the extent of daytime somnolence as reported by the score of the Epworth Sleepiness Scale (ESS). 3. verify feasibility to acquire dBM for motor symptoms (bradykinesia, tremor and dyskinesias, gait, posture) and non-motor symptoms (cognition)

	4. evaluate the performance of the dBMs correcting for age and sex.
OUTLINE OF THE RESEARCH	This is a multicentre observational research study. The study is conducted step-wise on two subsequent cohorts referred to as the development cohort (comprising 30 patients with RBD and 30 matched controls) and the confirmation cohort (comprising 30 patients with PD). Following a baseline visit, participants will undergo daily-life dBM tracking over a duration of 4 weeks and 3 months, respectively. Additionally, PD patients enrolled in the confirmation cohort will receive a polysomnography. The investigation is conducted in four European sites. Each site will submit this protocol to their local ethics committee.
Inclusion Criteria	**<u>Participants of the "Development cohort":</u>** **RBD patients:** ● Age: >18 years ● Written declaration of informed consent ● The participant is using a compatible smartphone, a smartwatch will be provided for the duration of the study ● The participant has a care partner with whom they share their bedroom at night ● Known RBD as defined by the International Classification of Sleep Disorders (ICSD-3) as demonstrated by polysomnography with at least one episode of RBD per week (on average over the last month, frequency reported with the help of the care partner). **Healthy matched controls:** ● Healthy volunteers demographically matched to the enrolled RBD patients. ● Written declaration of informed consent ● The participant is using a compatible smartphone; a smartwatch will be provided for the duration of the study.

	● No history of RBD. **<u>Participants of the "Confirmation cohort":</u>** ● Age: >18 years. ● Diagnosis of PD ● RBDSQ score 3 - 12 points ● Absence of dementia ● Written informed consent ● The participant is using a compatible smartphone, a smartwatch will be provided for the duration of the study ● Participants have a care partner.
Exclusion criteria	● Inability to consent for study procedures as judged by the investigator. ● Lacking motivation to participate in study procedures as judged by the investigator. ● Lack of social security.
Main Evaluation Criterion	As the primary outcome measure, we will determine the number of nights with dBM features reported by the smartwatch that in the development cohort correlated with the occurrence of RBD episodes. The study will be considered positive if RBD-associated features are not observed in at least 40% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD as confirmed by polysomnography.
Secondary Evaluation Criteria	- Spearman correlation coefficient between smartwatch-based features and the Epworth Sleepiness Scale (ESS) - continuity of motion tracking for analysis of motor dBM - number and quality of acquired videos for analysis of gait and posture - number of completed cognitive tasks - Correlation coefficients corrected for age and sex
Study size	A total of 90 participants will be enrolled in the study across the two subsequent cohorts, including 30 RBD patients and matched 30 controls in the "development cohort" and 30 patients with PD in the "confirmation cohort".

DURATION OF THE RESEARCH	**Development cohort:** - Duration of the recruitment period: 6 months - Follow-up period per participant: 4 weeks - Total research duration: 7 months **Confirmation cohort:** - Duration of the recruitment period: 6 months - Follow-up period per participant: 3 months - Total research duration: 9 months
STATISTICAL ANALYSIS OF THE DATA	Prof. Dr. med. Björn Falkenburger Klinik und Poliklinik für Neurologie Universitätsklinikum „Carl Gustav Carus“ Fetscherstraße 74 | 01307 Dresden
EXPECTED BENEFITS	It is hoped that the identification of robust dBMs in this study will have a favourable impact on the PD community in the future by enabling the daily-life detection and monitoring of PD symptoms, including the early signs of the disease such as RBD.

ABSTRACT

This research has been registered at http://www.clinicaltrials.gov/ on *date* under no. *number.*

Full title: AI-PROGNOSIS: Digital biomarkers development substudy (dBM-DEV study)

Simplified title: not required since <120 characters

This research is funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

- **Brief summary:** The main objective of this study is to identify features extracted from passive smartwatch data that are associated with episodes of REM sleep behaviour disorder (RBD) and demonstrate that these features can potentially help increase specificity of RBD detection as compared to the score of the RBD screening questionnaire (RBDSQ).
- **Detailed description:** RBD is the best predictor for neurodegenerative diseases with synuclein pathology, including Parkinson's disease (PD). RBD affects 0.5-1 % of the general population. It can only be diagnosed by polysomnography, which is a cumbersome procedure that cannot be used for screening. An RBD screening questionnaire (RBDSQ) has been developed which has high sensitivity but low specificity. Thus, to facilitate detection of prodromal PD, digital assessments can potentially be used to identify people with a high probability of RBD for polysomnography.
  The study is conducted step-wise on two subsequent cohorts referred to as the development cohort (comprising 30 patients with RBD and 30 matched controls) and the confirmation cohort (comprising 30 patients with PD). Following a baseline visit, participants will undergo daily-life dBM tracking over a duration of 4 weeks and 3 months, respectively. Additionally, PD patients enrolled in the confirmation cohort will receive a polysomnography.
- **Primary outcome:** The main objective of this study is to identify features extracted from passive smartwatch data that are associated with episodes of RBD and demonstrate that these features can potentially help increase specificity of RBD detection as compared to the score of the RBD screening questionnaire (RBDSQ).
- **Secondary outcomes:**
  - Demonstrate that sensitivity of RBD detection can be improved via dBM measurements as compared to the score of the RBD screening questionnaire;

- Identify mobility patterns (features) that correlate with the extent of daytime somnolence as reported by the score of the Epworth Sleepiness Scale (ESS);
- Verify feasibility to acquire dBM for motor symptoms (bradykinesia, tremor and dyskinesias, gait, posture) and non-motor symptoms (cognition);
- Evaluate the performance of the dBMs correcting for age and sex.

- **Study design:** This is a multicentre observational research study.
- **Eligibility criteria:**
    - **Inclusion criteria for participants of the "Development cohort":** Age: >18 years. RBD confirmed by polysomnography. The participant has a care partner with whom they share their bedroom at night. **Healthy controls**: demographically matched to enrolled RBD patients. No history of RBD.
    - **Inclusion criteria for participants of the "Confirmation cohort":** Age: >18 years. Diagnosis of PD. RBDSQ score of 3 - 12 points. Absence of dementia. The participant has a care partner.

  All participants must provide written informed consent. They must use a compatible smartphone; a smartwatch will be provided for the duration of the study.

    - **Exclusion criteria for both cohorts:** Inability to consent for study procedures as judged by the investigator. Lacking motivation to participate in study procedures as judged by the investigator.
- **Arm number or label and arm type:**
    - **Development cohort:** 30 patients with RBD, 30 matched controls
    - **Confirmation cohort:** 30 patients with PD
- **Interventions:** Clinical assessments, digital assessments using passive smartwatch data and active smartphone-based tests, polysomnography (confirmation cohort only)
- **Number of subjects:** 90
- **Statistical analysis:** As the primary outcome measure, we will determine the occurrence of night-time features that correlate with the occurrence of RBD episodes in the development cohort. The study will be considered positive if RBD-associated features are not observed in at least 40% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD as confirmed by polysomnography. In addition, we will determine Spearman correlation coefficients between features derived from smartwatch or smartphone and clinical scales, analyse extent and quality of motor and cognitive assessments.
- **Conditions:** Parkinson's disease, REM sleep behaviour disorder

- **Key-words:** Prodromal Parkinson's disease, digital assessments, home monitoring

2 SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1 Current state of knowledge

Parkinson's disease (PD) is the second most common neurodegenerative disease. It is caused by Lewy pathology spreading through the nervous system, which results in a number of motor and non-motor symptoms (Dinter et al. 2020). Digital technologies can potentially support diagnosis and treatment of PD by providing objective and continual data about motor and non-motor features of the disease. For instance, smartwatch-based features can be used for home-based reporting of motor fluctuations (Powers et al. 2021), tremor, dyskinesias (Sieberts et al. 2023), fine motor impairment (Iakovakis et al. 2018), but also for assessment of cognitive function (Dagum 2018).

The digital biomarker development (dBM-Dev) study presented here is part of a four-year HORIZON research programme entitled AI PROGNOSIS aiming to advance PD diagnosis and care by (1) developing novel, predictive AI models for personalised PD risk assessment and prognosis (in terms of time to higher disability transition and response to medication) based on multi-source patient records and databases, including in-depth health, phenotypic and genetic data, (2) implementing a system of digital biomarkers informing the AI models by tracking key risk/progression markers in daily living, and ultimately (3) translating the models and digital biomarkers into a validated, privacy-aware, AI-driven toolkit, supporting healthcare professionals (HCPs) in disease screening, monitoring and treatment optimization, via quantitative, explainable evidence, and empowering individuals with/without PD with tailored insights for informed health management.

Within this broader framework, the aim of the current dBM-DEV study is to develop the digital biomarkers that will be used in two subsequent well-powered clinical studies designed to validate the aforementioned AI-PROGNOSIS toolkit. Development of digital, home-based assessments for motor and cognitive function can build on a significant body of published evidence to which consortium partners have contributed (Dias et al. 2017; Mahboobeh et al. 2022; Dias et al. 2020; Iakovakis et al. 2018; 2020; Kyritsis, Diou, and Delopoulos 2019; Papadopoulos et al. 2020). In contrast, the literature about detection of (REM) sleep behaviour disorder (RBD) by digital, home-based assessments is much more limited. For this reason, development of a digital biomarker (dBM) for RBD was chosen as the primary objective of the dBM-DEV study, whereas the verification of dBMs for motor and cognitive symptoms are under secondary objectives.

RBD is the most important predictor for PD known today, and an accurate identification of individuals with prodromal PD is crucial to test and apply neuroprotective treatments.

RBD only affects 0.5-1 % of the general population (Sasai-Sakuma et al. 2020; Haba-Rubio et al. 2018; Kang et al. 2013). Current practice relies on a screening questionnaire and confirmation by polysomnography. The sensitivity of the RBD screening questionnaire (RBDSQ) is high (0.96) 9,19, but its specificity is only 0.56 (Stiasny-Kolster et al. 2007). This means that 44% of patients without RBD will have a positive RBDSQ. If one wanted to use the RBDSQ to detect RBD as a predictor for PD in the general population, 44% of the population would need to undergo polysomnography. This is not feasible due to cost and availability of sleep laboratories. In addition, the validity of the RBDSQ in early PD has been put into question (Halsband et al. 2018). Thus, there is thus a need for a confirmatory test to identify patients with a high risk for RBD to undergo polysomnography. One recent study used a three-step process based on an accelerometer and heart-rate data recorded from a smartwatch to first detect sleep/awake state, then identify the sleep stage, and finally movements during REM sleep (Ko et al. 2022; Auepanwiriyakul et al. 2020).

2.2. Research hypotheses

To be tested in the development cohort

In participants with known RBD, night-time mobility will be recorded using smartwatch inertial sensors. Features will be extracted from the raw data and analysed in concert with additional biomarkers (blood pressure, heart rate). We hypothesise that specific patterns of movement correlate with the occurrence of RBD episodes as reported with the help of care partners. This hypothesis also implies that these patterns are not detected in study participants without RBD.

Daytime mobility will also be recorded by the smartwatch inertial sensors. We hypothesise that specific patterns of reduced mobility correlate with the extent of daytime somnolence as reported by the score of the Epworth Sleepiness Scale (ESS). Similarly, we hypothesise that specific patterns of increased mobility correlate with the extent of tremor and dyskinesias as reported by the respective scores of the Movement Disorders Society - Unified Parkinson Disease Rating Scale (MDS-UPDRS).

In addition to these passive measurements, participants will also be given instructions to perform active motor tests related to posture, balance, gait, and leg agility. Skeleton tracking data will be collected from participants via smartphone camera. Finally, participants will be asked to perform short cognitive tests on their smartphone. Features extracted from this interaction with the smartphone include not only the percentage of correct answers, but also reaction times and their variances. These assessments for motor and non-motor symptoms of PD will be performed to verify feasibility of dBM assessment.

To be tested in the confirmation cohort:

The RBDSQ is a screening instrument. Hence it is characterised by high sensitivity and low specificity.

We will record passive data in study participants with an RBDSQ score of 3-12 points, thus around the cut-off value of 6 points. We hypothesise that the features extracted from these recordings can potentially help increase sensitivity and specificity of the RBDSQ. Specifically, we hypothesise that features associated with RBD episodes in the development cohort are not present in all participants with an RBDSQ score just above the cut-off, i.e. with 6-12 points. In addition, these features might be present in some of the participants with an RBDSQ score just below the cut-off, i.e., with 3-6 points.

Daytime mobility will again be recorded by the smartwatch inertial sensors. Any correlation observed between features of daytime mobility with daytime somnolence as reported by the ESS will be reassessed using the recordings obtained in the confirmation cohort. dBM for motor and non-motor symptoms of PD will be acquired as in the development cohort to verify feasibility of these assessments.

2.3. Justification of the methodological choices

Development cohort

RBD occurs at night and is characterised by movements of arms and legs during REM sleep. These movements cannot be detected by a smartphone alone; we will therefore supply study participants with a smartwatch (to be worn on the side where patients usually wear a watch). From the smartwatch, we will use the inertial sensors to detect the movements. In addition, we will use the recorded cordial data (e.g. heart rate) to properly attribute the movement to the correct sleep stages.

RBD episodes do not occur every night. In order to remain efficient and not burden participants unnecessarily, we will only include patients with more than 1 episode per week (on average).

RBD can only be detected with certainty in polysomnography. Yet, episodes do not occur every night and people often do not sleep well in the sleep lab. For this reason, we defined as the “ground truth” RBD episodes reported with the help of care partners in patients in which RBD was previously confirmed by polysomnography.

In order to support the identification of the correct stretches of the night, the first two participants will undergo polysomnography (at any time during the course of the study).

This will allow detection of the REM sleep phases and facilitate the development of the dBM.

Confirmation cohort

In order to remain efficient, we chose not to include patients in the confirmation cohort with a very high RBDSQ score. Because they already have a very high likelihood for RBD, adding a dBM is not likely to add relevant information. Similarly, we chose not to include participants with a very low score on the RBDSQ because they have a very low probability for RBD, and a dBM is unlikely to add relevant information.

In order to make sure participants can comply with study procedures, we chose to include only participants with MoCA > 24 points.

RBD episodes do not occur every night. In order to make sure the dBM has the potential to detect RBD episodes, the study duration was set to 3 months.

RBD is diagnosed by polysomnography. This diagnostic procedure was therefore chosen as the gold standard for the dBM development.

2.4. Expected benefits

It is hoped that the identification of robust dBMs in this study will have a favourable impact on the PD community in the future by enabling the daily-life detection and monitoring of PD symptoms, including the early signs of the disease such as RBD.

Objectives

Main objective

The main objective of this study is to identify a novel, robust dBM for the detection of RBD using smartwatch-based recordings of passive data.

Specifically, we aim to identify features extracted from passive smartwatch data collection that are associated with episodes of RBD and demonstrate that these features can potentially help increase specificity of RBD detection as compared to the score of the RBD screening questionnaire (RBDSQ).

The identified features will be independent of the device used for recording. One example could be the number of wrist movements during the second half of the night relative to the number of wrist movements during the first half of the night.

Secondary objectives

1. In extension to the primary objective, we aim to demonstrate that sensitivity of RBD detection can potentially be improved via dBM measurements as compared to the score of the RBD screening questionnaire.
2. We aim to identify mobility patterns (features) that correlate with the extent of daytime somnolence as reported by the score of the Epworth Sleepiness Scale (ESS)[10].
3. We aim to verify feasibility to acquire dBM for motor symptoms (tremor, bradykinesia, dyskinesias, gait, posture) and non-motor symptoms (cognition).
4. We aim to evaluate the performance of the dBMs correcting for age and sex.

3 Research design

AI-PROGNOSIS is a multicentre observational research study. The dBM-DEV substudy is conducted step-wise on two subsequent cohorts referred to as the development cohort (comprising 30 patients with RBD and 30 matched controls) and the confirmation cohort (comprising 30 patients with PD). Following a baseline visit, participants will undergo daily-life dBM tracking over a duration of 4 weeks and 3 months, respectively. Additionally, PD patients enrolled in the confirmation cohort will receive a polysomnography.

The investigation is conducted in four European sites (UK, France, Germany and Spain). Each site will submit this protocol to their local ethics committee.

Abbreviation	Site address	Principal Investigator
CHUT	CHU University Hospital Toulouse, place du Dr Baylac, 31059, Toulouse, France	Margherita Fabbri
FIN	Hospital Ruber Internacional, Calle La Masó 38, 28034, Madrid, Spain	Monica Kurtis
KCL	KING'S COLLEGE LONDON STRAND, LONDON WC2R 2LS,	Dhaval Trivedi

	United Kingdom	
TUD	Technische Universität Dresden Klinik für Neurologie Fetscherstrasse 74 Germany	Björn Falkenburger

5. ELIGIBILITY CRITERIA

5.1. Inclusion criteria

"Development cohort", inclusion criteria for participants with RBD

- Age: >18 years
- Written declaration of informed consent (see Annex 1).
- The participant is using a smartphone compatible with the smartwatch that will be provided for the duration of the study.
- The participant is able to use the smartphone, smartwatch and study app – as judged by investigator
- Wifi available at the participant's home to upload smartwatch data.
- Known RBD as defined by the *International Classification of Sleep Disorders (ICSD-3)* (Sateia 2014) confirmed by polysomnography
- The participant has a care partner with whom they share their bedroom at night
- Ability to provide information after each night whether an RBD episode occurred, with the help of their care partner
- At least one episode of RBD per week (on average over the last month).
- A diagnosis of PD is not required.

"Development cohort", inclusion criteria for controls

- Age (+/- 5 years)- and sex-matched control for a participant with known RBD
- Age: >18 years
- Written declaration of informed consent (see Annex 2).
- The participant is using a smartphone compatible with the smartwatch that will be provided for the duration of the study.

- The participant is able to use the smartphone, smartwatch and study app – as judged by investigator
- Wifi available at the participant's home to upload smartwatch data.

"Confirmation cohort", inclusion criteria for participants

- Age: >18 years.
- Diagnosis of PD based on the criteria published by the Movement Disorders Society (Postuma et al. 2015)
- Absence of dementia (defined as MoCA score ≥ 24) to ensure compliance with study procedures and ability to consent for study procedures. MoCA: Montreal Cognitive Assessment (Nasreddine et al. 2005)
- Written declaration of informed consent (see Annex 4)
- The participant is using a smartphone compatible with the smartwatch that will be provided for the duration of the study
- The participant has a care partner
- The participant is able to use the smartphone, smartwatch and study app – as judged by investigator
- RBDSQ score 3 - 12 points (Stiasny-Kolster et al. 2007)
- The medication for PD and sleep has not been changed during the past 4 weeks.
- Wifi available at the participant's home to upload smartwatch data.

Exclusion criteria, all cohorts

- Inability to consent for study procedures, e.g., due to cognitive decline, as judged by the investigator.
- Lacking motivation to participate in study procedures – as judged by the investigator.
- Participants who are not affiliated to their country's social security health system
- Participant under adult autonomy protection system, legal guardianship or incapacitation.

Feasibility and recruitment procedures

For both cohorts, participants will be recruited from the movement disorders outpatient clinics of the neurology department of each site. Healthy participants will be recruited by outreach activities that include conventional media (like newspapers) and social media. Material will be provided to the Ethics committee as it becomes available.

RBD only affects 0.5-1 % of the general population. In order to ensure a sufficiently high number of participants with RBD in the development cohort, we will mainly draw on the existing cohorts of RBD patients in each study site.

Procedures of the research

Screening and enrolment

Prospective participants will be informed about the study and will receive a participant information sheet and informed consent form approved by the appropriate ethics committee, describing the study, and providing sufficient information to allow them to make an informed decision about their participation, after adequate reflection time and prior to any assessment. If the participants have further questions about the study, these will be answered by the local study team at any time, on site or via remote communication (telephone or email).

Patients' care partners will be provided an information sheet explaining the study, as well as their role in helping patients provide the information required. The information sheet will include an optional statement of opposition, which care partners may sign should they object to the study.

After providing consent participants will be screened for inclusion and exclusion criteria. Gender will also be considered to ensure that groups are balanced, as a 1.5 to 1 ratio of male to female participants is foreseen, i.e., the same ratio observed for patients with PD in the general population.

In the confirmation cohort, after providing consent to participate in the study, patients will perform a MoCA test to confirm that dementia is not present. Results from a previous MoCA test may be used if collected less than 24 weeks prior to the patient signing the informed consent form. RBDSQ will be conducted after the MoCA. Patients with RBDSQ scores below 3 or above 12 will be excluded in order to avoid burdening patients with biomarker assessment and polysomnography for which dBMs are unlikely to change the result provided by the RBDSQ.

Study procedures in the development cohort

During baseline, the following demographic data will be registered: age, sex, education, handedness and ethnicity. The following assessments will be obtained:

- RBD screening questionnaire (RBDSQ) (Stiasny-Kolster et al. 2007)
- Epworth Sleepiness Scale (ESS) (Johns 1991)
- MDS-UPDRS I-IV, including the Hoehn and Yahr (HY) staging (Goetz et al. 2008)
- Parkinson's disease questionnaire, 8-item version (PDQ-8) (Peto et al., 1998)

If a participant is diagnosed with PD, the following information will be registered: year of first symptom, year of introduction of antiparkinsonian treatments, PD subtype (Stebbins et al. 2013), more strongly affected side, medication schedule.

The following commercially available smartwatch will be provided to each study participant with the official documentation (booklet): Withings Scanwatch (compatible with iOS and Android smartphones, see below for details), or equivalent. The study app will be installed on the participants' smartphone. This will be done by the study participant, with the support of study personnel if needed. The participant will be trained to set the time of day for the question about an RBD episode during the previous night. In addition, the Withings app will be installed on the participants' smartphone.

Each participant will be assigned a coded pseudonym consisting of the study site (e.g. "TUD") and a random number. This pseudonym will be noted on the enrolment log. This pseudonym will be used for registration on the study app and in the Withings app. No personal data (name, email, phone number) will be entered in either app. The study app is described in more detail below.

Participants will be instructed to wear the smartwatch as much as possible during day and night for 4 weeks. The predicted battery life for the smartwatch is 3 weeks. Every day, at a time specified by the study participants, they will be asked to respond with the help of their caregiver whether the likely had an episode of RBD during the previous night.

In addition, participants will perform active tests: Every two weeks, patients will be asked to acquire, with the help of their care partners, a short video of themselves while they tap their feet, rise from a chair, stand and walk. Moreover, patients will be asked to perform three brief cognitive tasks: N-back test, balloon analogue risk task, stop-signal task.

Data from smartwatch and smartphone will be transferred to the study cloud whenever the participant has access to wifi. An avatar will be fitted to each video after acquisition.

Only the avatar will be stored and transferred to the study cloud. Video data will not be stored in the study app or transmitted to the study cloud.

Patients will be called after 2 weeks by the study team to ask for problems or questions and every four weeks after that.

The first two patients of each study site will undergo polysomnography for one night to facilitate calibration of the digital biomarker for RBD. This will be scheduled based on availability during the course of the study.

At the end of the study, the smartwatch will be returned to the study centre and all apps will be uninstalled. If a participant is not able to return the smartwatch, they will be provided with a shipping envelope.

Study procedures in the confirmation cohort

A flowchart of the study procedures in the confirmation cohort is provided in Figure 1. Since the MoCA test for cognitive impairment is an exclusion criterion, but also a study procedure, it is performed after informed consent.

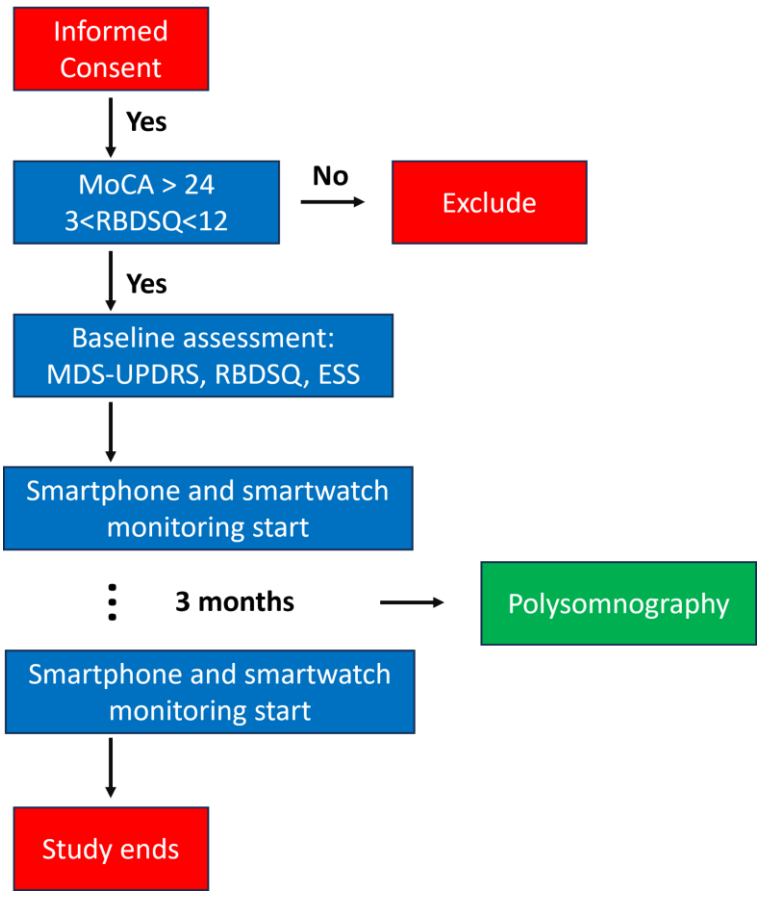


Figure 1: Flow of study procedures for the confirmation cohort

After providing informed consent, PD patients will be tested for cognition using the Montreal Cognitive Assessment (MoCA), version 7.1 with lion (Nasreddine et al. 2005). Patients with scores <24 will be excluded. Patients with scores >=24 will fill out the RBDSQ (Stiasny-Kolster et al. 2007). Patients with RBDSQ scores <3 and patients with scores >12 will be excluded. All other patients will undergo an assessment of general characteristics, including demographics (age, sex, education, handedness, ethnicity), year of first symptom, year of introduction of antiparkinsonian treatments, PD subtype (Stebbins et al. 2013), more strongly affected side, medication schedule.

Moreover, the following clinical assessments will be performed at baseline:

- MDS-UPDRS I-IV, including the Hoehn and Yahr (HY) staging (Goetz et al. 2008)
- Epworth Sleepiness Scale (ESS) (Johns 1991)
- Parkinson's disease questionnaire, 8-item version (PDQ-8) (Peto et al., 1998)

The following commercially available smartwatch will be provided to each study participant with the official documentation (booklet): Withings Scanwatch (compatible with iOS and Android smartphones, see below for details), or equivalent. The study app will be installed on the participants' smartphone. This will be done by the study participant, with the support of study personnel if needed. The participant will be trained to set the time of day for the question about an RBD episode during the previous night. In addition, the Withings app will be installed on the participants' smartphone.

Each participant will be assigned a coded pseudonym consisting of the study site (e.g. "TUD") and a random number. This pseudonym will be noted on the enrolment log. This pseudonym will be used for registration on the study app and in the Withings app. No personal data (name, email, phone number) will be entered in either app. The study app is described in more detail below.

Participants will be instructed to wear the smartwatch as much as possible during day and night for 3 months. The predicted battery life for the smartwatch is 3 weeks. Every day, at a time specified by the study participants, they will be asked to respond with the help of their caregiver whether the likely had an episode of RBD during the previous night.

In addition, participants will perform active tests: Every two weeks, patients will be asked to acquire, with the help of their care partners, a short video of themselves while they tap their feet, rise from a chair, stand and walk. Moreover, patients will be asked to perform three brief cognitive tasks: N-back test, balloon analogue risk task, stop-signal task.

Data from smartwatch and smartphone will be transferred to the study cloud whenever the participant has access to wifi. An avatar will be fitted to each video after acquisition.

Only the avatar will be stored and transferred to the study cloud. Video data will not be stored in the study app or transmitted to the study cloud.

Patients will be called after 2 weeks by the study team to ask for problems or questions and every four weeks after that.

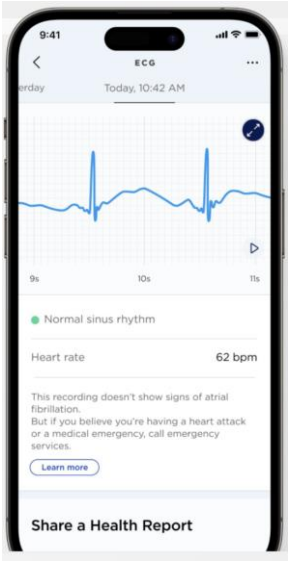
During the course of the study, each participant will undergo polysomnography. This will be scheduled during the 3 months period by study personnel.

At the end of the study, the smartwatch will be returned to the study centre and all apps will be uninstalled. If a participant is not able to return the smartwatch, they will be provided with a shipping envelope.

Description of the smartwatch

The Withings ScanWatch acquires 3-axis raw accelerometer data and raw multi-wavelength (green, red, infrared) photoplethysmography (PPG). It bears a CE mark but is not a medicinal product. Data will be transferred to the Withings app and uploaded to the Withings server. Each participant will be provided with a study-specific email address that will be used for registration, so their personal email address will not be shared with Withings. The raw data will be transferred from the Withings server to the dBM-DEV study server through the Withings Advanced Research API. Withings servers are located in BSO data centres in France. Measures for data security are described below.

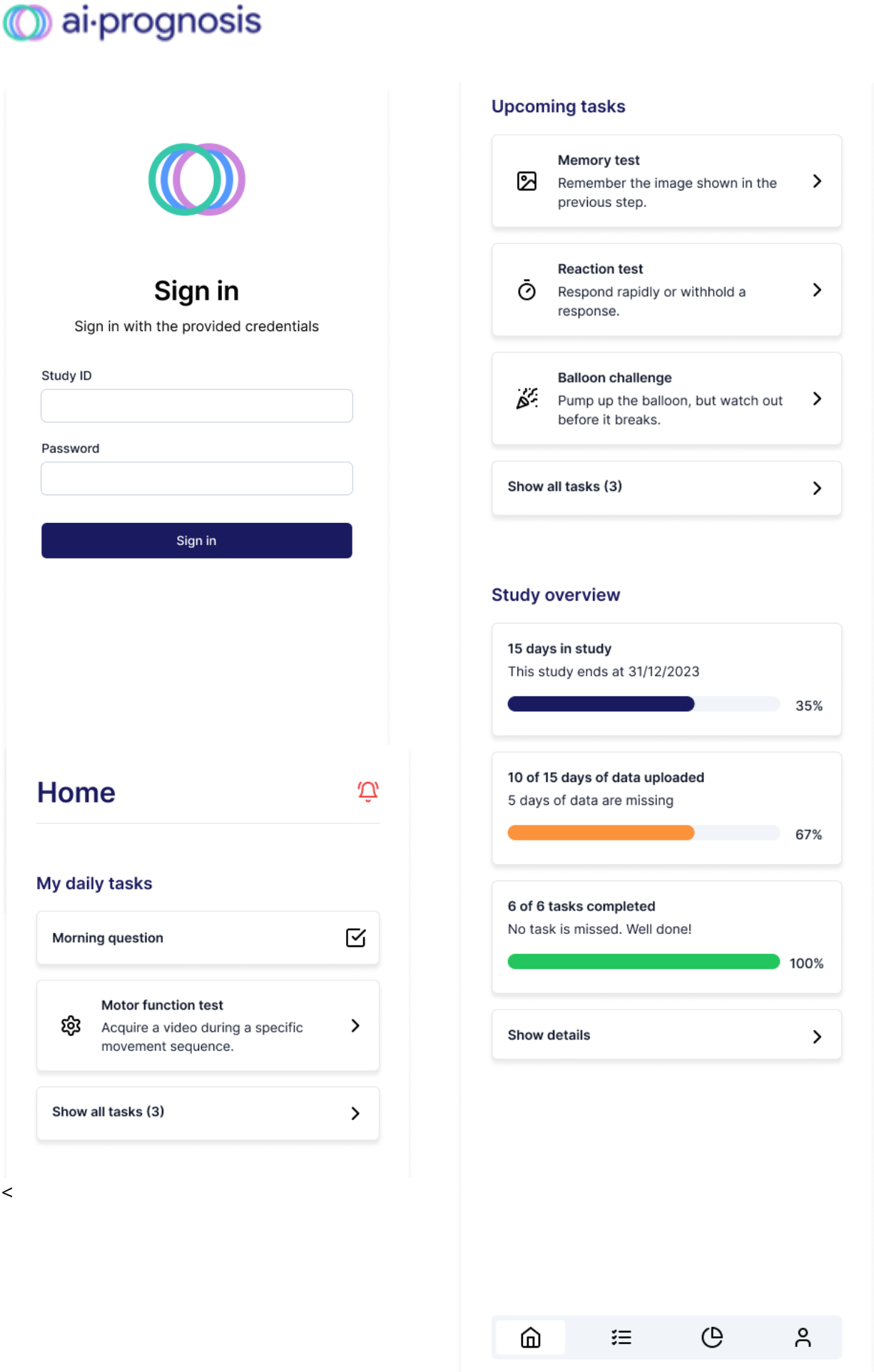
ScanWatch smartphone



Withings app

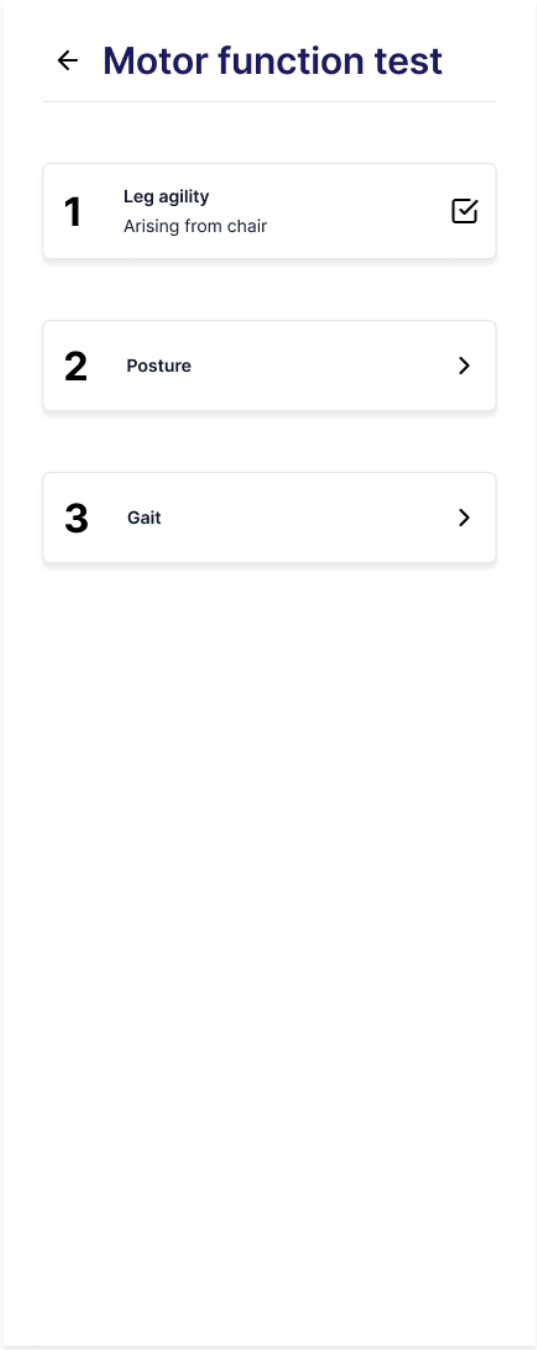
Description of the study app

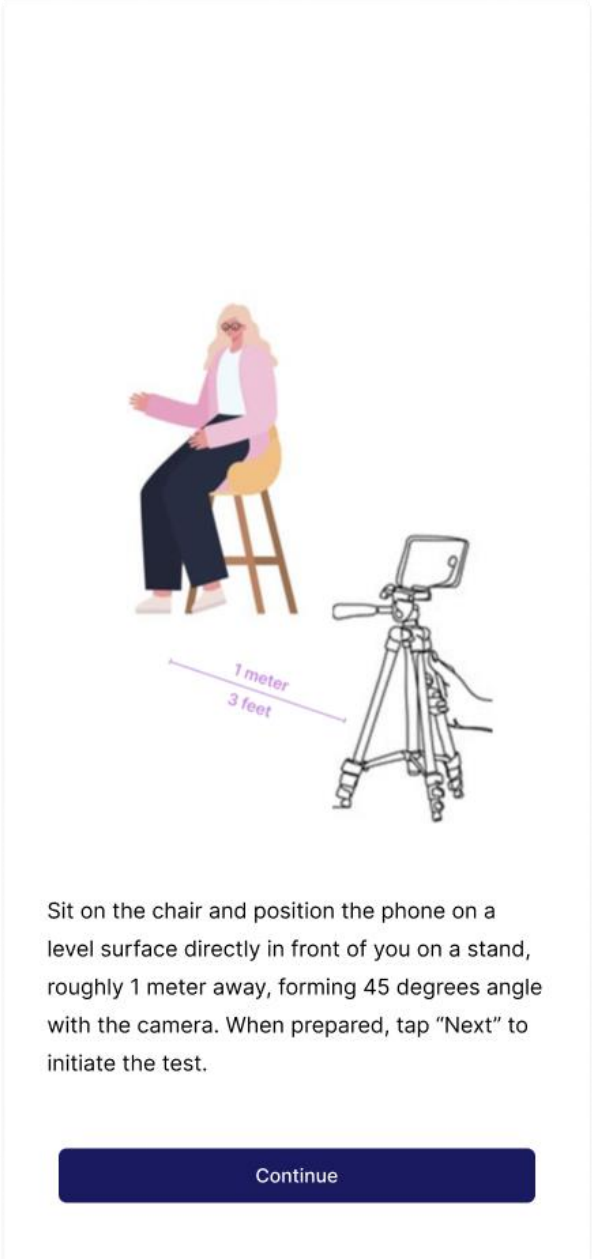
The dBM-DEV study app was developed by Squaredev (Brussels, Belgium). It will be installed on the participants' personal smartphone. The study ID will be used for registration. No personal data (name, phone number, …) will be stored in the app or transmitted to the study cloud. The study is available in three languages for the participant to choose: English, French, German, Spanish. Screenshots are shown in English.

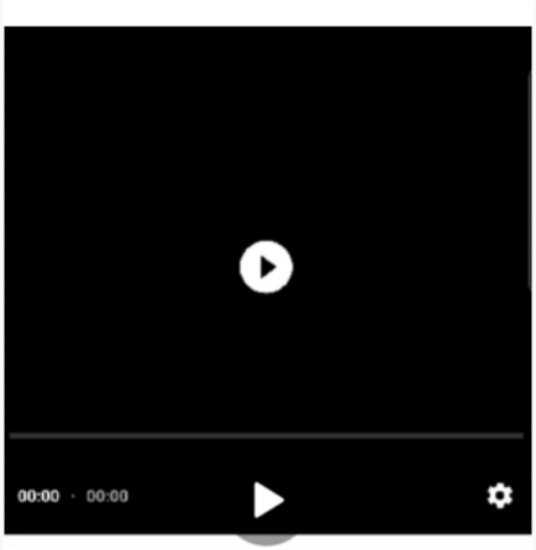

ai·prognosis
Sign in
Sign in with the provided credentials
Study ID
Password
Sign in
Upcoming tasks
Memory test
Remember the image shown in the previous step.
Reaction test
Respond rapidly or withhold a response.
Balloon challenge
Pump up the balloon, but watch out before it breaks.
Show all tasks (3)
Study overview
15 days in study
This study ends at 31/12/2023
35%
10 of 15 days of data uploaded
5 days of data are missing
67%
6 of 6 tasks completed
No task is missed. Well done!
100%
Show details
Home
My daily tasks
Morning question
Motor function test
Acquire a video during a specific movement sequence.
Show all tasks (3)

<

Every two weeks, patients will be asked to acquire, with the help of their care partners, a short video of themselves while they perform a motor function test (45° angle, see screenshots below): Participants should sit on the chair and place both feet on the floor. First, tap each leg separately ten times. Next, with hands placed on the chest, participants should rise from the chair, maintain a standing position for 5 seconds. Lastly, they should take three steps forward, turn around, and return to the initial standing position. The sequence concludes with the participants returning to the seated position.







Motor test recorded

Well done

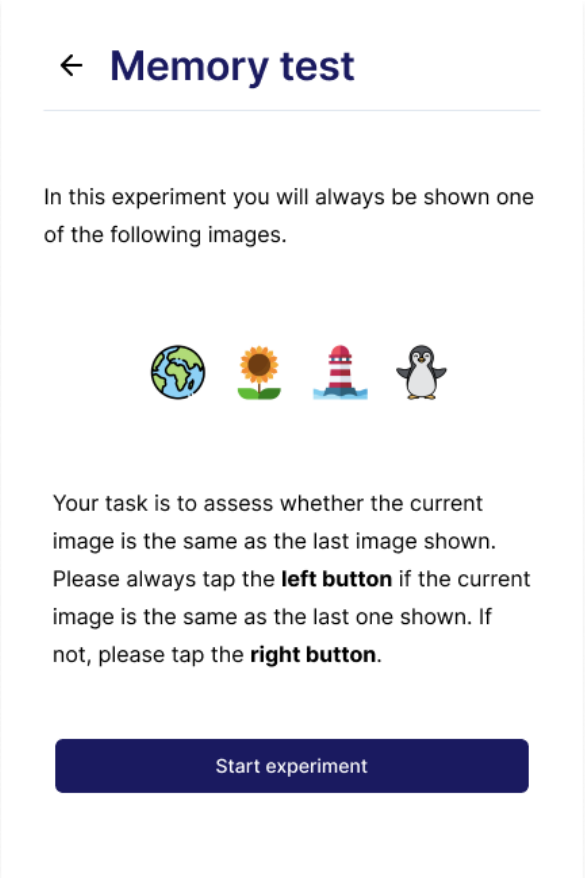
Repeat Exit

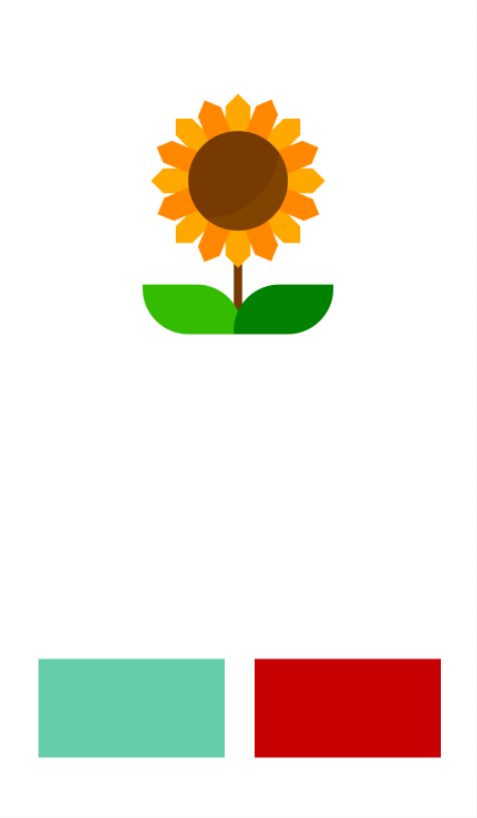
Sit on the chair with both feet on the floor. Tap each leg 10 times quickly, separately. Then, stand from the chair with your hands on chest and maintain a standing position for 5 seconds. Take 3 steps forward, turn around, return to starting position, and sit back down slowly to complete the sequence.

Back Start test

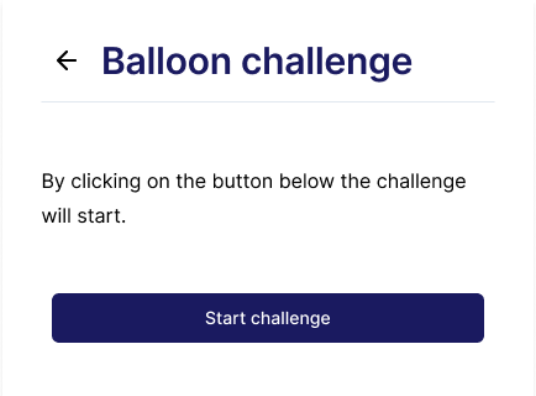
Moreover, patients will be asked to perform three brief cognitive tasks:

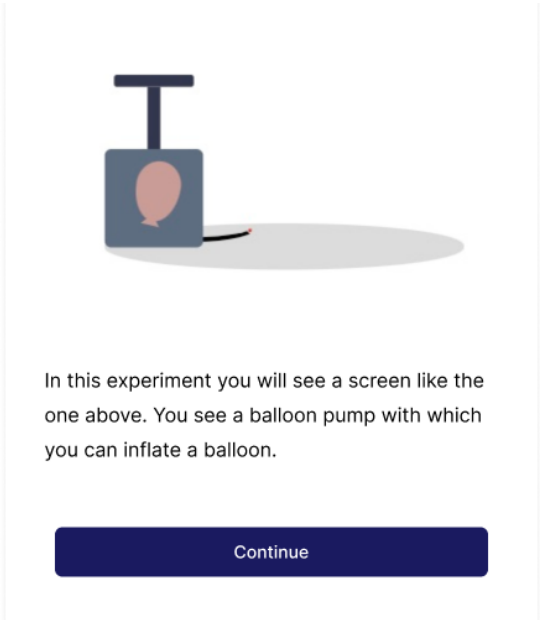
The N-back task examines working memory (Kirchner 1958). The subject is presented with a sequence of stimuli, and the task consists of indicating when the current stimulus matches the one from 1 step (generally n steps) earlier in the sequence. The response is indicated by tapping either the green or the red button on the screen.

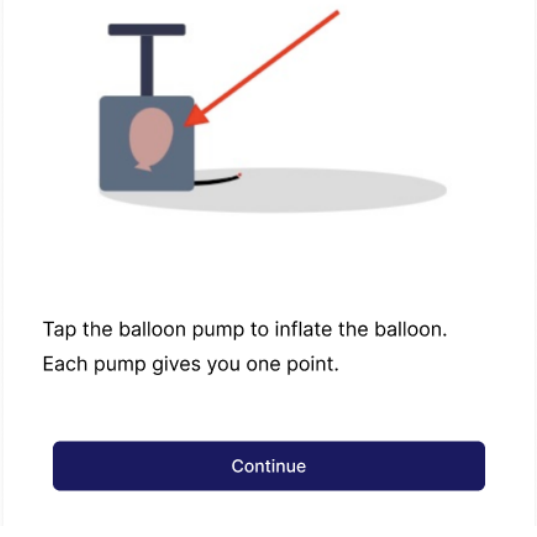




The balloon analogue risk task (BART) is a computerised decision-making task that is used to assess risk-taking behaviour (Lejuez et al. 2002). During the task, a participant is presented with 90 balloons of 3 different colours. The balloons appear one at a time. Participants are required to click a button labelled 'Balloon Pump.' Each click on the balloon pump will increase the size of the balloon and accumulate 5 cents per click in a temporary bank. The participants are not shown the amount being accumulated in their temporary bank. At any time, the participant can press another tab, labelled 'Collect $,' to transfer the collected money into a permanent bank. If the participant wishes to continue pumping the balloon, they can do so, until eventually, the balloon explodes, resulting in the temporary funds resetting to zero and the next balloon showing up. However, if the participant collects the money before the balloon explodes, they can see the amount earned on that particular balloon via the tab labelled 'Last Balloon.' The money in the permanent bank will not be lost when a balloon explodes. Overall, the BART measures the risk-taking behaviour of an individual by recording the average number of pumps for each balloon colour, the total amount of earnings, and the number of exploded balloons.

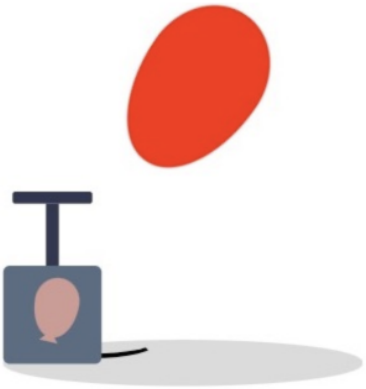






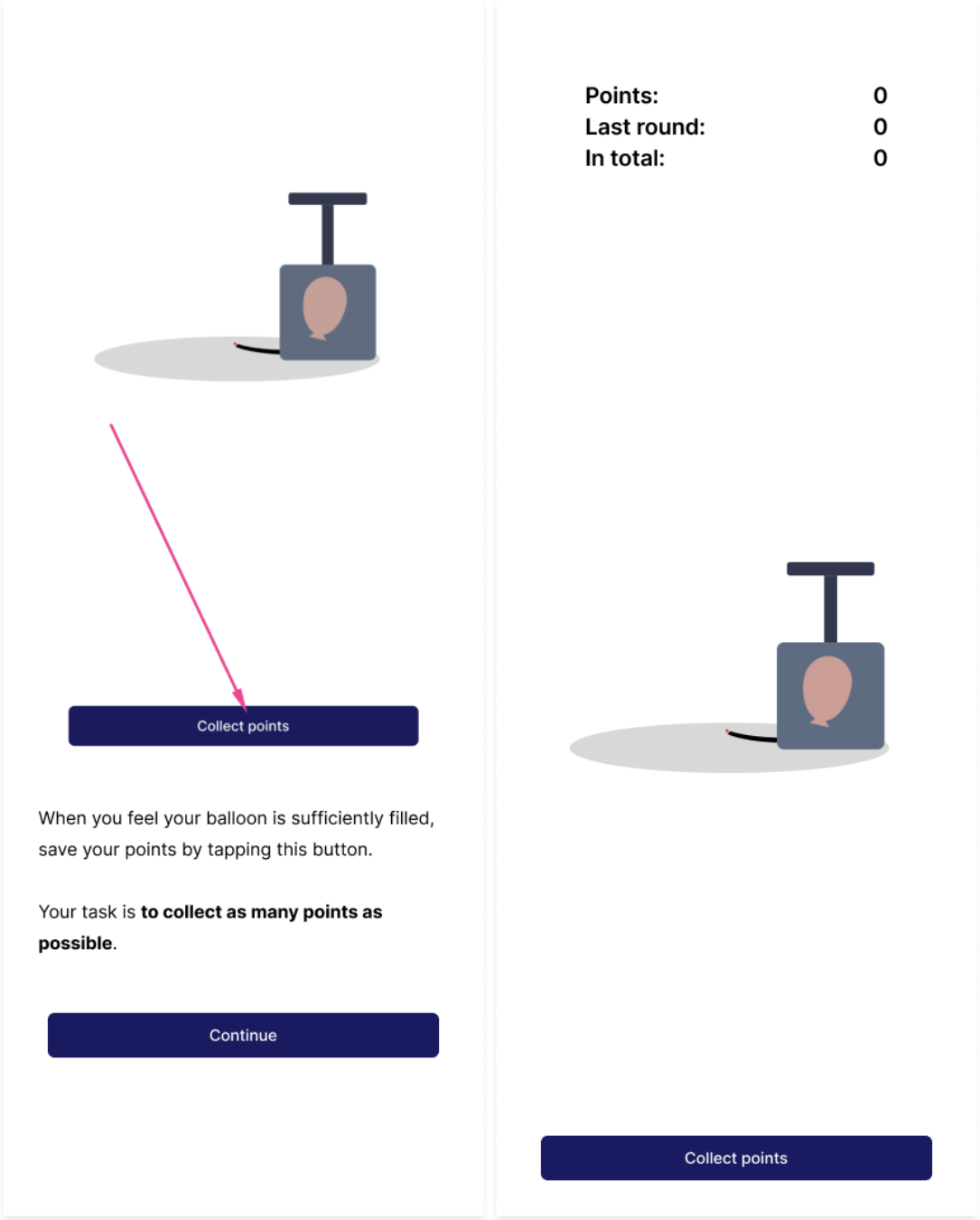
For example, if you pumped 30 times, you have **theoretically** collected 30 points.

Continue

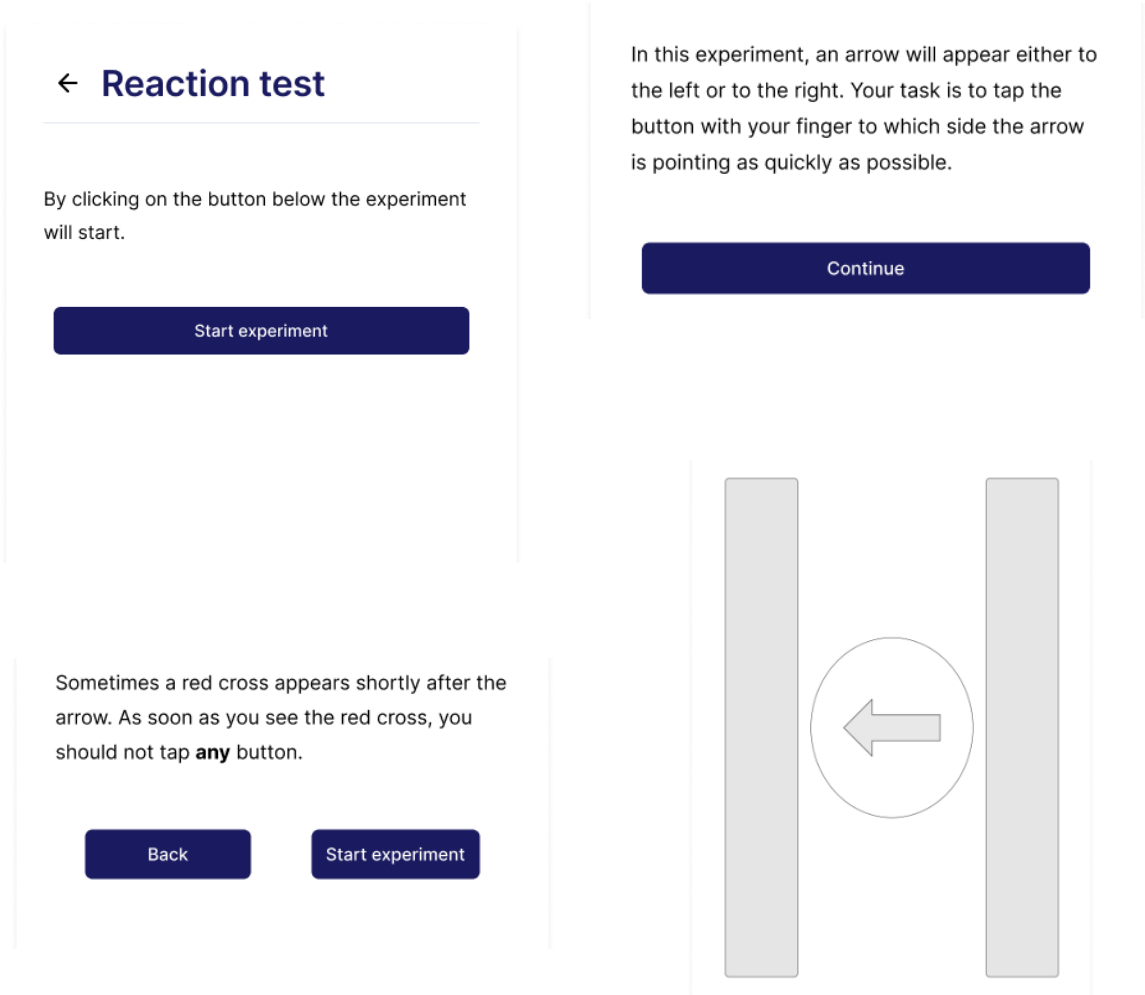


Attention: If you pump too much, the balloon will fly away and your points will be lost.

Continue


Collect points
When you feel your balloon is sufficiently filled, save your points by tapping this button.
Your task is to collect as many points as possible.
Continue
Points: 0
Last round: 0
In total: 0
Collect points

The stop-signal task measures attention (Lappin and Eriksen 1966) and is influenced by dopaminergic signalling (Colzato et al. 2009; Choudhury et al. 2019) and has been applied in mobile form (He et al. 2022). The participant must respond to an arrow stimulus, by selecting one of two options, depending on the direction in which the arrow points. If an audio tone is present, the subject must withhold making that response (inhibition). The test consists of two parts: In the first part, the participant is introduced to the test and told to select the left-hand button when they see a left-pointing arrow and the right-hand button when they see a right-pointing arrow. There is one block of 16 trials for the participant to practise this. In the second part, the participant is told to continue selecting the buttons when they see the arrows but, if they hear an auditory signal (a beep), they should withhold their response and not select the button. The task uses a staircase design for the stop signal delay (SSD), allowing the task to adapt to the performance of the participant, narrowing in on the 50% success rate for inhibition.



Data from the smartphone will be transferred to the study cloud whenever the participant has access to wifi. An avatar will be fitted to each video after acquisition. Only the avatar will be stored and transferred to the study cloud. Video data will not be stored in the study app or transmitted to the study cloud.

Possible complications/risks

The active tests performed by patients during the study are not riskier than movements carried out during their daily routine. They can be discontinued at any time or omitted if deemed not feasible by the participant.

Withdrawal

Participants will be able to withdraw their consent at any time and without giving any reason. In such a case, data collected up to that point in time will be kept in a pseudonymized form and used for the purposes of the study, unless participants exercise their right under the GDPR for their data to be deleted.

Participants who withdraw from the study or do not adhere to study procedures, e.g., do not use the smartphone app or the smartwatch, do not complete the questionnaires, or change their medication without authorisation from the investigator, will be replaced by recruiting new subjects.

EVALUATION CRITERIA

7.1. Main evaluation criterion

As an outcome measure, we will determine in study participants with high RBDSQ score the number nights with features that in the development cohort correlated with the occurrence of RBD episodes.

We expect these RBD-associated features to be more common in participants with a high RBDSQ score (7-12 points) than in participants with a low RBDSQ score (3-6 points). We also expect RBD-associated features to be more common in participants in which RBD is diagnosed by polysomnography than in participants in which this diagnosis is not made.

The study will be considered positive if the following conditions are met:

- RBD-associated features are observed in all participants with an RBDSQ score above the threshold of 6 points and a diagnosis of RBD in polysomnography.
- RBD-associated features are not observed in participants with an RBDSQ score below the threshold of 6 points and no diagnosis of RBD in polysomnography.
- RBD-associated features are not observed in at least 40% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD in polysomnography.

In this case, we will conclude that the new dBM can potentially be used to detect RBD with higher **specificity** than the RBDSQ.

7.2. Secondary evaluation criteria

1. In extension to the main evaluation criterion, we will conclude that the new dBM can potentially be used to detect RBD with higher **sensitivity** than the RBDSQ if the following criteria are met:
   - RBD-associated features as defined by dBM tracking are observed in all participants with an RBDSQ score above the threshold of 6 points and a diagnosis of RBD in polysomnography.
   - RBD-associated features are not observed in participants with an RBDSQ score below the threshold of 6 points and no diagnosis of RBD in polysomnography.
   - RBD-associated features are not observed in at least 20% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD in polysomnography.

2. With respect to the dBM for daytime somnolence, we will define mobility patterns (features) based on smartphone accelerometer data in the development cohort that correlate with the ESS score. In the confirmation cohort, we will measure the extent of the same features. Spearman correlation coefficients with the ESS score will be calculated for these features. This secondary end point will be considered met if the correlation is significant ($p < 0.05$) with $r^2 > 0.70$.

3. To verify feasibility for dBM assessment of bradykinesia, dyskinesias and tremor, we will quantify the amount of time that the smartwatch was worn during each day of the study and whether known motor signatures of bradykinesia, dyskinesias and tremor can be extracted from the data. As exploratory endpoints, we will determine the

correlation between dBM and the corresponding score of the MDS-UPDRS obtained during the baseline visit.

4. To verify feasibility for dBM assessment of posture and gait, we will determine the number of videos acquired and their quality. Specifically, we will determine whether an avatar can be fitted to the videos. As an exploratory endpoint, we will correlate the obtained dBM score with the score obtained by a trained human rater.

5. To verify feasibility for dBM assessment of cognitive performance, we will determine the number of completed cognitive tasks. As an exploratory endpoint, we will determine whether task results correlate to the cognitive performance as assessed by MoCA during the baseline visit.

6. With respect to age and sex, all correlations listed above will be repeated with correction for age and sex. This is an exploratory readout.

CONDUCTING the research

The research schedule

Development cohort:

- Duration of the recruitment period: 6 months
- Follow-up period per participant: 4 weeks
- Total research duration: 7 months

Confirmation cohort:

- Duration of the recruitment period: 6 months
- Follow-up period per participant: 3 months
- Total research duration: 9 months

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Summary table of the participant follow-up

Development cohort

	Screening	Baseline[3]	During 4 weeks period[4]
Informed consent	X		
Inclusion / exclusion criteria	X		
Sex	X		
Demographics[1]		X	
RBDSQ		X	
ESS		X	
PD clinical information[2]		X	
MDS-UPDRS I-IV		X	
PDQ-8		X	
Install App		X	
Hand out smartphone		X	
Smartwatch accelerometer data			Continually (as much as possible, allow time for charging the device)
Active motor tests			Every two weeks (+/- two days)
Cognitive tests			Every two weeks (+/- two days)
Polysomnography			Once[5] (scheduling based on availability)
Question about previous night			Once daily at time specified by user

1) age, sex, education, handedness

2) For participants with PD only: year of first symptom, year of introduction of antiparkinsonian treatments, PD subtype, more strongly affected side, medication schedule

3) Screening and baseline can be on the same day. Maximum delay between Screening and baseline is 4 weeks.

4) Delay between baseline and end of study is 4 weeks +/- 7 days

5) If one of the first two participants per site.

Confirmation cohort

	Screening	Baseline[3]	During 3 months period[4]
Informed consent	X		
Inclusion / exclusion criteria	X		
Sex	X		
MoCA	X		
RBDSQ	X		
Demographics[1]		X	
PD clinical information[2]		X	
MDS-UPDRS I-IV		X	
PDQ-8		X	
ESS		X	
Install App		X	
Hand out smartphone		X	
Smartwatch accelerometer data			Continually (as much as possible, allow time for charging the device)
Active motor tests			Every two weeks (+/- two days)
Cognitive tests			Every two weeks (+/- two days)
Polysomnography			Once (scheduling based on availability)
Question about previous night			Once daily at time specified by user

1) age, sex, education, handedness

2) year of first symptom, year of introduction of antiparkinsonian treatments, PD subtype, more strongly affected side, medication schedule

3) Screening and baseline can be on the same day. Maximum delay between Screening and baseline is 4 weeks.

4) Delay between baseline and end of study is 3 months +/- 7 days

Information of the persons concerned

The doctor will invite the patient to participate in this research and will inform him/her of the objective, the digital processing of data concerning the patient that will be collected during this research and will also specify the patient's rights of access, opposition and rectification to these data.

The doctor will also check the eligibility criteria. If the patient agrees to participate, he/she will orally give his/her consent and his/her non-opposition is documented in his/her medical file. The participant may, at any time, object to the use of his/her data as part of the research.

STATISTICAL ASPECTS

Calculation of study size

This is an exploratory study, and we have insufficient data for a precise sample size estimation.

Previous studies investigating sensitivity of the RBDSQ included 54 and 30 patients with RBD9,19. We will use comparable numbers for the development cohort and include 30 patients with confirmed RBD and 30 controls that are matched for age and sex.

The sample size of 30 patients for the confirmation cohort is based on the number of realistic polysomnography investigations performed at each site, the available resources and polysomnography capacities.

Statistical methods employed

Primary evaluation criteria

We will determine the number of nights with RBD-associated dBM features.

The study will be considered positive if the following conditions are met:

1. RBD-associated features are observed in all participants with an RBDSQ score above the threshold of 6 points and a diagnosis of RBD in polysomnography.
2. RBD-associated features are not observed in participants with an RBDSQ score below the threshold of 6 points and no diagnosis of RBD in polysomnography.
3. RBD-associated features are not observed in at least 40% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD in polysomnography.

<u>Rationale for choosing these conditions:</u>

The sensitivity of the RBDSQ is stated in the literature as 96% (Stiasny-Kolster et al. 2007; Halsband et al. 2018). We therefore expect that all patients with RBD in polysomnography

will also have a positive RBDSQ score of >6 points. The new digital biomarker should have the same good sensitivity as the RBDSQ. Therefore, the first criterion for a positive study is that the digital biomarker is also detectable in all patients in whom RBD can be detected on polysomnography (and an RBDSQ score >6 is to be expected).

The specificity of the RBDSQ is cited as 56%. We therefore expect that about half of the patients without RBD will show an RBDSQ score of >6 points in the polysomnography and the other half <6 points. As the specificity of the new digital biomarker should not be lower than that of the RBDSQ, the second criterion for a positive study is that of the patients without RBD who are correctly categorised by the RBDSQ (score <6), the digital biomarker is (also) undetectable.

As the specificity of the new digital biomarker should be higher than that of the RBDSQ, the third criterion is that the digital biomarker is not detectable in at least 40% of patients without RBD who are not correctly categorised by the RBDSQ (false-positive RBDSQ score >6).

This increase by 40% was chosen as follows to obtain a statistically significant improvement of diagnostic accuracy as determined by McNemar's test.

The prevalence of RBD in patients with Parkinson's disease is 25%. Of the 30 participants included in the Confirmation Cohort, 7 probably will have RBD and 23 will not have RBD. Due to the high sensitivity of the RBDSQ, all 7 participants with RBD are expected to have an RBDSQ score >6, and following criterion 1, they will be dBM-positive. Among the 23 participants without RBD, the above numbers suggest that 10 will have a (false-positive) RBDSQ score >6 and 13 will have a (correct-negative) RBDSQ score <6.

The following table summarizes these numbers assuming that n participants that are false-positive in RBDSQ will be (correctly) negative in the dBM.

	RBDSQ correct	RBDSQ incorrect
dBM correct	20 (7 positive[1] + 13 negative)	n
dBM incorrect	0	10-n

Whether a change in the detection of an RBD is statistically significant can now be compared with the McNemar test with c = RBDSQ-positive, dBM negative; b = RBDSQ-negative, dBM positive:

n	**$\chi^2 = (\|b-c\|)^2/(b+c)$**	**Evaluation**
1	1	n.s.
2	2	n.s.
3	3	n.s.
4	4	p<0.05
5	5	p<0.05

At 5% error probability and 1 degree of freedom, values χ2 above 3.84 are statistically significant.

Hence, based on the McNemar test, dBM will represent a statistically significant improvement if at least 4 of the 10 patients (40%) with false-positive RBDSQ are negative in the digital biomarker.

Secondary evaluation criteria

1. Similarly, we will determine whether the following criteria are met:
   - RBD-associated features as defined by dBM tracking are observed in all participants with an RBDSQ score above the threshold of 6 points and a diagnosis of RBD in polysomnography.
   - RBD-associated features are not observed in participants with an RBDSQ score below the threshold of 6 points and no diagnosis of RBD in polysomnography.
   - RBD-associated features are not observed in at least 20% of participants with an RBDSQ score above the threshold of 6 points but no diagnosis of RBD in polysomnography.
2. We will measure the frequency of features associated with daytime somnolence in the development cohort. Spearman correlation coefficients with the ESS score will be calculated. This secondary end point will be considered met if the correlation is significant ($p < 0.05$) with $r^2 > 0.70$.
3. We will quantify the amount of time that the smartwatch was worn during each day of the study and whether known motor signatures of bradykinesia, dyskinesias and tremor can be extracted from the data.
4. We will determine the number of videos acquired and whether an avatar can be fitted to the videos.
5. All correlations listed above will be repeated with correction for age and sex.

Exploratory analyses

1. We will measure the frequency of features associated with bradykinesia, tremor and dyskinesias in the development cohort. Spearman correlation coefficients with the score of the MDS-UPDRS item will be calculated for these features. This secondary end point will be considered met if the correlation is significant ($p < 0.05$) with $r^2 > 0.70$.
2. We will manually score by trained raters and also by an algorithm trained in the development. Spearman correlation coefficients between the two scores will be calculated. This set of secondary end points will be considered met if the correlation is significant ($p < 0.05$) with $r^2 > 0.70$.
3. Features obtained from the smartphone-based cognitive tests will be determined from both cohorts, pooled and correlated to the MoCA of the same participant at baseline. This set of secondary end points will be considered met if the correlation is significant ($p < 0.05$) with $r^2 > 0.70$.

Rights of access to data and source documents

Legal basis of data processing

Participants will provide written informed consent for all acquisition, storage and processing of data. If participants withdraw consent, the data will be deleted.

Only personal data will be recorded that is strictly necessary for an outcome or for the quality control of the research.

Subjects may request the deletion of their data at any time, even without giving reasons. Data that have already been included in evaluations or have been anonymised can no longer be deleted.

Moreover, for the purposes of ensuring personal data protection and integrity, a data processing agreement has been signed between the partners, defining the data that will be processed, the envisaged processing operations, the allocation of tasks and operations between the partners, possible data transfers between the partners, the envisaged storage period of the data, the implemented technical and organisational measures.

All data collected is for scientific purposes only. The findings from this research project will be published exclusively in an anonymised form. It is ensured that the re-identification of individual patients is not possible.

Access to data

Agreeing to participate in the protocol implies that the people who carry out the research will make the documents and personal data that are strictly necessary for the monitoring, quality control and auditing of the research, available in accordance with the laws and regulations in force.

Source data

All information contained in original documents, or in authenticated copies of these documents, relating to clinical examinations, observations or other activities conducted as part of a research and necessary for the reconstruction and evaluation of the research. The documents in which the source data are saved are called the source documents.

The following data are considered source data:

- Informed consent
- Patient questionnaires

All other data are digital data or entered into the eCRF directly:

- Presence or absence of inclusion and exclusion criteria
- Demographics
- PD clinical information (for participants with a diagnosis of PD)
- Smartwatch accelerometer data
- Data recorded during active tests on the smartphone

Data confidentiality

In accordance with the legislative provisions in force, persons having direct access to source data will take all the necessary precautions to ensure the confidentiality of information relating to research, to participants, especially as regards their identity and the results obtained. These people, like the people who direct and monitor the research, are subject to professional secrecy.

All data stored in eCRF and all digital data is codified. The names of the persons concerned or their addresses are never mentioned.

Participants will be assigned a study-specific pseudonym upon inclusion, which does not allow any inference to their person ("TUD" and random number). The list for identifying patients (enrolment log) is stored exclusively on the study PI's local computer and is not passed on to cooperation partners. Access to the enrolment log is limited to the local study team, i.e., employees of TUD financed by the Horizon AI-PROGNOSIS project.

At the end of the study, the data that allows identification of a participant (enrolment log) will be deleted. The records are then anonymised and will be kept in this form indefinitely. The data subjects will be also informed regarding this final processing operation.

The sponsor will ensure that each research participant has been informed of access to the individual data concerning them and strictly necessary for the quality control of the research.

Quality control and quality assurance

Guidelines for collecting data

For each participant enrolled, an eCRF must be completed and signed by the principal Investigator or authorised (PI-delegated) from the study staff. The Investigator should ensure the accuracy, completeness and timeliness of the data in the eCRFs and in all required reports. A clinical research technician will enter the data into the eCRF database created by the data manager in charge of the study. dBM data will be collected via smartwatch and smartphone. An explanation must be provided for any missing data.

Management of the research

Research will be conducted by the investigator in accordance with a clinical research technician (study coordinator). This technician will be in charge of:

- logistics and the organisation of the patients visits (calls and preparation of study procedures)
- reporting on the study progress to the sponsor
- completing the case report form (request for additional information, corrections, etc.),
- participating in monitoring visits with the Clinical Research Associate appointed by the sponsor.

The clinical research technician will work in accordance with the standard operating procedures (GCP).

Monitoring of the research

The Sponsor or the Sponsor's representative will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

Monitoring and auditing procedures developed by the Sponsor or the Sponsor's representative will be followed in order to comply with GCP guidelines. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

A clinical researcher appointed by the sponsor who is not directly involved in the study will regularly visit the study team, during the implementation of the research, one or more times during research.

- after enrolment of the first participant
- in accordance with the risk-based monitoring plan during the course of the study
- at the end of the study

During these visits and in accordance with the risk-based monitoring plan, the following elements will be reviewed:

- informed consent,
- compliance with the research protocol and the procedures defined therein,
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the source documents

All visits will be the subject of a monitoring report by written report.

Data management

Electronic case report form (eCRF)

Open Clinica will be used for the eCRF. Data will be entered into the eCRF by qualified and delegated site personnel (clinicians or study coordinator of the site).

Aristotle University of Thessaloniki, the coordinator of the overarching Horizon AI-PROGNOSIS project, will be responsible for hosting and maintaining the database on a server located in France.

TUD will be in charge of data management for this study. The data manager will generate a validation plan that will have to be approved by the scientific council of the study. After data capture, with the help of AUTH, the data manager will generate a set of validation tests that will aim at verifying respect of inclusion / exclusion criteria, identifying missing data, checking chronologic consistency when several dates are considered, and highlighting aberrant data. Following these tests, a set of queries will be sent to the

investigators for verification and whenever it is possible for correction. Then, the database will be corrected accordingly, before locking the database for data analysis.

Means of security

Infrastructure security features that could be implemented include: firewall protection of infrastructure serves, DDoS attack protection, authenticated access to infrastructure servers, identity and access management of services/tools, reverse proxy configuration for services/tools, encrypted and secure communication with infrastructure servers and deployed tools, hard disk encryption of infrastructure servers if required, backups and snapshots of infrastructure servers, Hetzner-provided additional security features (data centres certified according to ISO/IEC 27001)

Management of access right

The management of access rights will be enforced with the deployment of an authentication-authorization server, like Keycloak. There, each user will be assigned with a study-specific pseudonym/account and a corresponding password that could be set to respect enhanced security rules, e.g., 8 characters minimum, containing at least three of specific character types such as upper case, lower case, numbers and/or special characters etc.

Backups and snapshots of infrastructure servers

Hetzner, the cloud provider, offers backups of the VMs hosting the servers periodically, on a daily time basis. For each server, there are seven slots for backups kept in Hetzner servers. If all slots are full, the oldest backup will be deleted. The backups are kept in Hetzner servers in the same geographic location as the cloud server they were created from, but usually in a different data centre. In addition, Hetzner offers custom snapshots whose creation and deletion is not automatic and can be initiated only by the user/customer. Snapshots are automatically in a different location than the cloud server they were created from but in the same network zone.

Audit and inspection

An audit may be conducted at any time by persons appointed by the sponsor and independent of the persons conducting the research. Its purpose is to verify the

participants' safety and respect for their rights, compliance with applicable regulations and the reliability of data.

An inspection can also be carried out by a competent authority (e.g., EMA in the context of a European study).

The audit, as well as the inspection, can be applied at all stages of the research, from the development of the protocol to the publication of the results and the classification of the data used or produced as part of the research.

Investigators agree to comply with the sponsor's requirements as regards an audit and the competent authority for a research inspection.

Ethical AND REGULATORY considerations

Compliance with reference texts

The planning, implementation and use of the project and the project results will be in accordance with the relevant ethical and scientific standards. During the course of the study, the partners will respect the fundamental principles of research integrity, as set out in the European Code of Conduct for Research Integrity, thus respecting human dignity and integrity, ensuring honesty and transparency towards research subjects and by receiving freely provided and informed consent (as well as assent whenever relevant), protecting vulnerable people, ensuring privacy and confidentiality, promoting justice and inclusiveness, minimising harm and maximising benefit and sharing the benefits with disadvantaged populations or any people who will be benefited by its findings and results.

The applicants thus undertake to comply with the requirements of the Memorandum on Safeguarding Good Scientific Practice of the German Research Foundation (DFG), the Declaration of Helsinki and Memorandum III "Methods for Health Services Research" (Dietrich et al., 2010) of the German Network for Health Services Research, the State or Federal Data Protection Act and the General Data Protection Regulation of the European Parliament and of the Council (Regulation EU 2016/679 - GDPR). In addition, the clinically active colleagues involved follow the professional regulations for physicians of the responsible state medical association in the respective current versions.

The study plan is submitted to the Ethics Committee of the University Hospital Dresden for consultation before the start of the study.

The names of the patients and all other confidential information are subject to the medical confidentiality obligation of the attending physicians and the provisions of the

General Data Protection Regulation and the Federal Data Protection Acts (DSGVO and BDSG new).

Benefit-Risk ratio

No risks are expected for participating in this study, Participants have no direct benefit from participating in the study except for the control group for which detection of paradoxical sleep disorder is possible. Moreover, participating in a research study can increase self-efficacy and sense of control for study participants.

Constraints related to the research and possible compensation of participants

Participants are not allowed to enrol simultaneously in other intervention trials and will be notified accordingly. They will be allowed to enrol in other trials as soon as their enrolment in the current study comes to an end. The only constraint for patients is having to wear the watch day and night, and having to complete the tests required as part of the study protocol. Participants only travel once to the centre, at study initiation, except for 1) participants whose screening and baseline visits cannot be performed on the same day, and 2) patients who carry out a polysomnography, which is performed on a separate visit.

Participants who complete the entire study will receive a compensation of €100.

4 Bibliography

Auepanwiriyakul, Chaiyawan, Sigourney Waibel, Joanna Songa, Paul Bentley, and A. Aldo Faisal. 2020. "Accuracy and Acceptability of Wearable Motion Tracking for Inpatient Monitoring Using Smartwatches." *Sensors* 20 (24): 7313. https://doi.org/10.3390/s20247313.

Choudhury, Supriyo, Akash Roy, Banashree Mondal, Ravi Singh, Saptak Halder, Koustav Chatterjee, Mark R. Baker, Hrishikesh Kumar, and Stuart N. Baker. 2019. "Slowed Movement Stopping in Parkinson's Disease and Focal Dystonia Is Improved by Standard Treatment." *Scientific Reports* 9 (1): 19504. https://doi.org/10.1038/s41598-019-55321-5.

Colzato, Lorenza Serena, Wery P. M. van den Wildenberg, Nelleke C. van Wouwe, Merel M. Pannebakker, and Bernhard Hommel. 2009. "Dopamine and Inhibitory Action Control: Evidence from Spontaneous Eye Blink Rates." *Experimental Brain Research* 196 (3): 467–74. https://doi.org/10.1007/s00221-009-1862-x.

Dagum, Paul. 2018. "Digital Biomarkers of Cognitive Function." *NPJ Digital Medicine* 1: 10. https://doi.org/10.1038/s41746-018-0018-4.

Dias, S. B., E. Konstantinidis, J. A. Diniz, P. Bamidis, V. Charisis, S. Hadjidimitriou, M. Stadtschnitzer, et al. 2017. "On Supporting Parkinson's Disease Patients: The i-Prognosis Personalized Game Suite Design Approach." In *2017 IEEE 30th International Symposium on Computer-Based Medical Systems (CBMS)*, 521–26. Thessaloniki, Greece: IEEE. https://doi.org/10.1109/CBMS.2017.144.

Dias, Sofia Balula, Athina Grammatikopoulou, José Alves Diniz, Kosmas Dimitropoulos, Nikos Grammalidis, Vicky Zilidou, Theodore Savvidis, et al. 2020. "Innovative Parkinson's Disease Patients' Motor Skills Assessment: The i-PROGNOSIS Paradigm." *Frontiers in Computer Science* 2 (July): 20. https://doi.org/10.3389/fcomp.2020.00020.

Dinter, Elisabeth, Theodora Saridaki, Leonie Diederichs, Heinz Reichmann, and Björn H. Falkenburger. 2020. "Parkinson's Disease and Translational Research." *Translational Neurodegeneration* 9 (1): 43. https://doi.org/10.1186/s40035-020-00223-0.

Goetz, Christopher G., Barbara C. Tilley, Stephanie R. Shaftman, Glenn T. Stebbins, Stanley Fahn, Pablo Martinez-Martin, Werner Poewe, et al. 2008. "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results." *Movement Disorders: Official Journal of the Movement Disorder Society* 23 (15): 2129–70. https://doi.org/10.1002/mds.22340.

Haba-Rubio, José, Birgit Frauscher, Pedro Marques-Vidal, Jérôme Toriel, Nadia Tobback, Daniela Andries, Martin Preisig, Peter Vollenweider, Ronald Postuma, and Raphaël Heinzer. 2018. "Prevalence and Determinants of Rapid Eye Movement Sleep Behavior Disorder in the General Population." *Sleep* 41 (2): zsx197. https://doi.org/10.1093/sleep/zsx197.

Halsband, Claire, Antonia Zapf, Friederike Sixel-Döring, Claudia Trenkwalder, and Brit Mollenhauer. 2018. "The REM Sleep Behavior Disorder Screening Questionnaire Is Not Valid in De Novo Parkinson's Disease." *Movement Disorders Clinical Practice* 5 (2): 171–76. https://doi.org/10.1002/mdc3.12591.

He, Jason L., Rebecca J. Hirst, Rohan Puri, James Coxon, Winston Byblow, Mark Hinder, Patrick Skippen, et al. 2022. "OSARI, an Open-Source Anticipated Response Inhibition Task." *Behavior Research Methods* 54 (3): 1530–40. https://doi.org/10.3758/s13428-021-01680-9.

Iakovakis, Dimitrios, K. Ray Chaudhuri, Lisa Klingelhoefer, Sevasti Bostantjopoulou, Zoe Katsarou, Dhaval Trivedi, Heinz Reichmann, Stelios Hadjidimitriou, Vasileios Charisis, and Leontios J. Hadjileontiadis. 2020. "Screening of Parkinsonian Subtle Fine-Motor Impairment from Touchscreen Typing via Deep Learning." *Scientific Reports* 10 (1): 12623. https://doi.org/10.1038/s41598-020-69369-1.

Iakovakis, Dimitrios, Stelios Hadjidimitriou, Vasileios Charisis, Sevasti Bostantzopoulou, Zoe Katsarou, and Leontios J. Hadjileontiadis. 2018. "Touchscreen Typing-Pattern Analysis for Detecting Fine Motor Skills Decline in Early-Stage Parkinson's Disease." *Scientific Reports* 8 (1): 7663. https://doi.org/10.1038/s41598-018-25999-0.

Johns, M. W. 1991. "A New Method for Measuring Daytime Sleepiness: The Epworth

Sleepiness Scale." *Sleep* 14 (6): 540–45. https://doi.org/10.1093/sleep/14.6.540.
Kang, Suk-Hoon, In-Young Yoon, Sang Don Lee, Ji Won Han, Tae Hui Kim, and Ki Woong Kim. 2013. "REM Sleep Behavior Disorder in the Korean Elderly Population: Prevalence and Clinical Characteristics." *Sleep* 36 (8): 1147–52. https://doi.org/10.5665/sleep.2874.
Kirchner, W. K. 1958. "Age Differences in Short-Term Retention of Rapidly Changing Information." *Journal of Experimental Psychology* 55 (4): 352–58. https://doi.org/10.1037/h0043688.
Ko, Yi-Feng, Pei-Hsin Kuo, Ching-Fu Wang, Yu-Jen Chen, Pei-Chi Chuang, Shih-Zhang Li, Bo-Wei Chen, et al. 2022. "Quantification Analysis of Sleep Based on Smartwatch Sensors for Parkinson's Disease." *Biosensors* 12 (2): 74. https://doi.org/10.3390/bios12020074.
Kyritsis, Konstantinos, Christos Diou, and Anastasios Delopoulos. 2019. "Modeling Wrist Micromovements to Measure In-Meal Eating Behavior From Inertial Sensor Data." *IEEE Journal of Biomedical and Health Informatics* 23 (6): 2325–34. https://doi.org/10.1109/JBHI.2019.2892011.
Lappin, Joseph S., and Charles W. Eriksen. 1966. "Use of a Delayed Signal to Stop a Visual Reaction-Time Response." *Journal of Experimental Psychology* 72 (6): 805–11. https://doi.org/10.1037/h0021266.
Lejuez, C. W., Jennifer P. Read, Christopher W. Kahler, Jerry B. Richards, Susan E. Ramsey, Gregory L. Stuart, David R. Strong, and Richard A. Brown. 2002. "Evaluation of a Behavioral Measure of Risk Taking: The Balloon Analogue Risk Task (BART)." *Journal of Experimental Psychology. Applied* 8 (2): 75–84. https://doi.org/10.1037//1076-898x.8.2.75.
Mahboobeh, Dunia J., Sofia B. Dias, Ahsan H. Khandoker, and Leontios J. Hadjileontiadis. 2022. "Machine Learning-Based Analysis of Digital Movement Assessment and ExerGame Scores for Parkinson's Disease Severity Estimation." *Frontiers in Psychology* 13 (March): 857249. https://doi.org/10.3389/fpsyg.2022.857249.
Nasreddine, Ziad S., Natalie A. Phillips, Valérie Bédirian, Simon Charbonneau, Victor Whitehead, Isabelle Collin, Jeffrey L. Cummings, and Howard Chertkow. 2005. "The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment." *Journal of the American Geriatrics Society* 53 (4): 695–99. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
Papadopoulos, Alexandros, Konstantinos Kyritsis, Lisa Klingelhoefer, Sevasti Bostanjopoulou, K. Ray Chaudhuri, and Anastasios Delopoulos. 2020. "Detecting Parkinsonian Tremor From IMU Data Collected In-the-Wild Using Deep Multiple-Instance Learning." *IEEE Journal of Biomedical and Health Informatics* 24 (9): 2559–69. https://doi.org/10.1109/JBHI.2019.2961748.
Postuma, Ronald B., Daniela Berg, Matthew Stern, Werner Poewe, C. Warren Olanow, Wolfgang Oertel, José Obeso, et al. 2015. "MDS Clinical Diagnostic Criteria for Parkinson's Disease." *Movement Disorders: Official Journal of the Movement Disorder Society* 30 (12): 1591–1601. https://doi.org/10.1002/mds.26424.
Powers, Rob, Maryam Etezadi-Amoli, Edith M. Arnold, Sara Kianian, Irida Mance, Maxsim Gibiansky, Dan Trietsch, et al. 2021. "Smartwatch Inertial Sensors Continuously

Monitor Real-World Motor Fluctuations in Parkinson's Disease." *Science Translational Medicine* 13 (579): eabd7865. https://doi.org/10.1126/scitranslmed.abd7865.

Sasai-Sakuma, Taeko, Noboru Takeuchi, Yasuhiro Asai, Yuichi Inoue, and Yosuke Inoue. 2020. "Prevalence and Clinical Characteristics of REM Sleep Behavior Disorder in Japanese Elderly People." *Sleep* 43 (8): zsaa024. https://doi.org/10.1093/sleep/zsaa024.

Sateia, Michael J. 2014. "International Classification of Sleep Disorders-Third Edition: Highlights and Modifications." *Chest* 146 (5): 1387–94. https://doi.org/10.1378/chest.14-0970.

Sieberts, Solveig K., Henryk Borzymowski, Yuanfang Guan, Yidi Huang, Ayala Matzner, Alex Page, Izhar Bar-Gad, et al. 2023. "Developing Better Digital Health Measures of Parkinson's Disease Using Free Living Data and a Crowdsourced Data Analysis Challenge." *PLOS Digital Health* 2 (3): e0000208. https://doi.org/10.1371/journal.pdig.0000208.

Stebbins, Glenn T., Christopher G. Goetz, David J. Burn, Joseph Jankovic, Tien K. Khoo, and Barbara C. Tilley. 2013. "How to Identify Tremor Dominant and Postural Instability/Gait Difficulty Groups with the Movement Disorder Society Unified Parkinson's Disease Rating Scale: Comparison with the Unified Parkinson's Disease Rating Scale." *Movement Disorders: Official Journal of the Movement Disorder Society* 28 (5): 668–70. https://doi.org/10.1002/mds.25383.

Stiasny-Kolster, Karin, Geert Mayer, Sylvia Schäfer, Jens Carsten Möller, Monika Heinzel-Gutenbrunner, and Wolfgang H. Oertel. 2007. "The REM Sleep Behavior Disorder Screening Questionnaire--a New Diagnostic Instrument." *Movement Disorders: Official Journal of the Movement Disorder Society* 22 (16): 2386–93. https://doi.org/10.1002/mds.21740.

ai·prognosis

Patient information and consent form for the
non-interventional observational research study for

" Digital biomarkers development, validation and verification (dBM-DEV) "

Development cohort: Participants with RBD

Dear participant,

Because you have been diagnosed with REM sleep behaviour disorder (RBD), we are asking you whether you would like to participate in our study. This study is testing whether RBD can be detected by information recorded by a smartwatch. Please read this patient information carefully and feel free to ask us for further information.

Aim of the study

Neuroprotective treatments will be most useful if administered early in the course of any neurodegenerative disease. Several neurodegenerative diseases, including Parkinson's disease, are preceded by a prodromal phase, a phase of first symptoms announcing the actual illness. This prodromal phase is characterised by specific symptoms, including RBD. As you know people with RBD may scream or kick their feet during sleep, sometimes falling out of bed or hurting people sleeping close to them.
RBD is not a common condition, affecting only one in 100-200 people. And RBD can only be diagnosed with certainty in a sleep lab. Probably, you have already been to a sleep lab. Hence you know that in a sleep lab, people need to be in the hospital for one or two nights with wires recording heart rate, blood pressure, movements and brain waves (EEG). This is cumbersome, and not everyone can be admitted to a sleep lab. In order to find people with RBD more easily, a screening tool has been developed. It is called the RBD screening questionnaire (RBDSQ).
Yet, the RBDSQ is not perfect; among 100 people where RBD can be suspected based on the RBDSQ, only 42 will actually have RBD when they undergo investigation in the sleep lab. So the sleep lab investigation will not be necessary for more than half of the people with a positive RBDSQ. In order to improve finding people with RBD, and in order to reduce the number of people undergoing investigation in a sleep lab, we want to use digital biomarkers recorded by a smartwatch.

Procedure of the study

This study is conducted in parallel with four other European sites. In each site, 30 participants will be enrolled.
The study will be conducted over a total period of four weeks. If you participate in the study, we will provide you with a smartwatch free of charge for the study period. We will perform an initial assessment, which takes about 30 minutes. Specifically, we will ask you about general information (age, year of first symptoms, handedness, …) and conduct the following scales that are standard for patients with PD to complete:

- Cognitive test (MoCA)

- Screening questionnaire for REM sleep behaviour disorder (RBDSQ)
- Questionnaire about sleepiness (Epworth Sleepiness Scale)
- Standard motor examination (MDS-UPDRS)

We will then ask you to install the study App on your smartphone and to set up the smartwatch using the operating instructions. This will include the installation of the smartphone app. A study supervisor is available to help you here at any time. You can also contact us in case of technical problems at any time during the course of the study.
The smartwatch will record the movements of your arm during sleep, and also other data like blood pressure and heart rate. The information will be transmitted to your smartphone. From the smartphone it will be transmitted to the study cloud whenever your smartphone is connected to a free wireless network.
After each night, the smartphone App will ask you and your caregiver if you think that an episode of RBD has occurred. This will make it easier for our data analysts to identify the important pieces of data in the recordings. Based on these recordings, they will then develop an algorithm that can detect RBD just based on the smartwatch data.
If you are one of the two first participants of the study, we will ask you to spend one night in the hospital for polysomnography as you previously did when your REM sleep behaviour disorder was first diagnosed.
Every two weeks, you will be asked to use your smartphone to record a video (1 min maximum duration) while standing, rising from a chair, walking away from the camera and back, tapping your left and right leg. To preserve your privacy, an avatar will be fitted to each video after acquisition. Only the avatar will be stored and transferred to the study cloud. Video data will not be stored in the study app or transmitted to the study cloud.
Finally, you will be asked to complete three short cognitive tasks every two weeks. They require less than 15 minutes in total.
The data recorded by the smartwatch will be stored on your smartphone and transmitted to the study cloud whenever you have wifi access.
The study team will call you after 2 weeks to ask whether everything works well, and every four weeks after taht.
After 4 weeks, you will return the smartwatch to the study centre and deinstall the App.

Conditions of participation

Your participation in the study is voluntary. Your treatment will not be affected by the study. You confirm your willingness to participate by signing this document, a copy of which will be given to you. You can withdraw your consent to the study at any time without having to give us a reason, and without any further disadvantages for the future treatment of your disease.
You are not expected to benefit directly from your participation in the study. However, you can contribute to finding patients with RBD more easily in the future by participating in this trial.
We cannot offer you any remuneration for your voluntary participation in the study.

Ethical and legal issues

The researchers involved in the study follow the principles described in the latest version of the Declaration of Helsinki. The study was reviewed by the ethics committee of the TU Dresden and approved for implementation.

Risks

No risks are expected by participating in this study.

Data protection

In this study, your personal data will be stored. Your name and the month and year of birth are recorded in a document termed enrollment log. This is the only place. It is a paper document stored in a folder in the study centre and only study personnel have access to the folder. In all other places, your personal data (age, year of diagnosis, smartwatch data) is only identified by code or pseudonym (e.g. DD1234) from which you cannot be identified.
The smartphone data is stored on a dedicated server together with your pseudonym. During transfer to the server, the data is encrypted, and it is also stored in encrypted form.
Different partners of the AI-PROGNOSIS project are involved in analysing the smartphone data, but they can only see your code and not your real name. Only people with access to the enrollment log can know whose data it is.
The following partners will receive data and participate in data analysis:

- ARISTOTELEIO PANEPISTIMIO THESSALONIKIS (AUTH), with legal address KEDEA BUILDING, TRITIS SEPTEMVRIOU, ARISTOTLE UNIVERSITY CAMPUS, THESSALONIKI 546 36, Greece
- AINIGMA TECHNOLOGIES (AING), with legal address KAPELDREEF 60, LEUVEN 3001, Belgium,
- CENTRE HOSPITALIER UNIVERSITAIRE DE TOULOUSE (CHUT), with legal address 2 RUE VIGUERIE HOTEL DIEU SAINT JACQUES, TOULOUSE CEDEX 9 31059, France,
- ETHNIKO KENTRO EREVNAS KAI TECHNOLOGIKIS ANAPTYXIS (CERTH), with legal address CHARILAOU THERMI ROAD 6 KM, THERMI THESSALONIKI 57001, Greece,
- FACULDADE DE MOTRICIDADE HUMANA (FMH), with legal address ESTRADA DA COSTA, CRUZ QUEBRADA LISBOA 1495-688, Portugal,
- FUNDACION INICIATIVA PARA LAS NEUROSCIENCIAS - FOUNDATION FOR INITIATIVES IN NEUROSCIENCE (FIN), with legal address CALLE REVENTON 11, MADRID 28002, Spain,
- KATHOLIEKE UNIVERSITEIT LEUVEN (KUL), for the purposes of this agreement represented by KU Leuven Research & Development, with legal address WAAISTRAAT 6 – BOX 5105, LEUVEN 3000, Belgium,
- KING'S COLLEGE LONDON (KCL), with legal address STRAND, LONDON WC2R 2LS, United Kingdom
- NETCOMPANY-INTRASOFT SA (INTRA), with legal address RUE NICOLAS BOVE 2B, LUXEMBOURG 1253, Luxembourg,
- SQUAREDEV (SQD), with legal address KANTERSTEEN 47, BRUSSELS 1000, Belgium,
- TECHNISCHE UNIVERSITAET DRESDEN (TUD), with legal address HELMHOLTZSTRASSE 10, DRESDEN 01069, Germany,

All participating partners are subject to the European Data Protection Regulation. The legal basis for data processing is your consent (Article 9(2)(a) and Article 6(1)(a) of the European Data Protection Regulation).
The Department of Neurology of the Medical Faculty Carl Gustav Carus Dresden is responsible for processing your patient data. The responsible data protection officer can be reached at:

University Hospital Carl Gustav Carus Dresden, Data Protection Officer
Fetscherstrasse 74
01307 Dresden
E-mail: DSV@uniklinikum-dresden.de

You also have the possibility to file a complaint with any data protection supervisory authority.
You have the right to obtain information about the data that is related to you. You have the right to receive your data in a standardised electronic format or to have it transferred to an office named by you (right to data portability).

Right to object

Your consent is voluntary!
You can completely revoke your consent to further participation in this study at any time without giving reasons and without any adverse consequences for you. A revocation always refers only to the future use of your patient data. Data from analyses that have already been carried out cannot be subsequently removed.
For a revocation, please contact the principal investigator indicated below under Contact.

Contact

If you have any further questions or problems, you can contact the principal investigator at any time:
Prof. Dr. med. Björn Falkenburger
Klinik und Poliklinik für Neurologie
Universitätsklinikum Carl Gustav Carus
an der Technischen Universität Dresden
Fetscherstraße 74
01307 Dresden
Email: bfalken@ukdd.de
Tel: 0351 458 2532

Informed consent for the research study for

" Digital biomarkers development, validation and verification (dBM-DEV) "

Development cohort: Participants with RBD

I give my consent to participate in the above non-invasive study. I understand that my participation is voluntary. I may withdraw my consent at any time without prior notice and without giving reasons, without any disadvantage to me.

In addition, I declare my consent to the following data protection provisions:

a. I agree that some of the data collected in the study, in particular my health information, gender and age, will be provided by code number only and will be recorded in computers, stored and processed for scientific purposes in the context of the present study.

b. In case of publication of research results, the data will only be used in coded form. No results allow the identification of the person.

c. Anonymised data will be made available to the scientific communing according to the FAIR principles.

I have received the written patient information about the above research project and have been given a copy of my signed consent form to participate.

Yes, I would like to participate in the study.

No, I do not want to take part in the study.

_____
(name of the study participant)

_____
(date & signature study participant)

_____
(name of the investigator)

_____
(signature and stamp of investigator)

Information leaflet

" Digital biomarkers development, validation and verification (dBM-DEV) "

Development cohort: Care person

Dear participant,

You are caring for or living with a potential participant of the " Digital biomarkers development, validation and verification (dBM-DEV)" study. This study is testing whether RBD can be detected by information recorded by a smartwatch.
He/she is free to participate or not. We ask that you do not verbally object to her/his participation, because your role will be important for the study to run smoothly. You can take as much time as you need to read the information below and ask any questions you may have to the research doctor, known as the investigator.

Aim of the study

Neuroprotective treatments will be most useful if administered early in the course of any neurodegenerative disease. Several neurodegenerative diseases, including Parkinson's disease, are preceded by a prodromal phase, a phase of first symptoms announcing the actual illness. This prodromal phase is characterised by specific symptoms, including RBD. As you know people with RBD may scream or kick their feet during sleep, sometimes falling out of bed or hurting people sleeping close to them.
RBD is not a common condition, affecting only one in 100-200 people. And RBD can only be diagnosed with certainty in a sleep lab. Probably, you have already been to a sleep lab. Hence you know that in a sleep lab, people need to be in the hospital for one or two nights with wires recording heart rate, blood pressure, movements and brain waves (EEG). This is cumbersome, and not everyone can be admitted to a sleep lab. In order to find people with RBD more easily, a screening tool has been developed. It is called the RBD screening questionnaire (RBDSQ).
Yet, the RBDSQ is not perfect; among 100 people where RBD can be suspected based on the RBDSQ, only 42 will actually have RBD when they undergo investigation in the sleep lab. So the sleep lab investigation will not be necessary for more than half of the people with a positive RBDSQ. In order to improve finding people with RBD, and in order to reduce the number of people undergoing investigation in a sleep lab, we want to use digital biomarkers recorded by a smartwatch.

Procedure of the study

This study is conducted in parallel with four other European sites. In each site, 30 participants will be enrolled.
The study will be conducted over a total period of four weeks. If the person you care for participates in the study, we will provide him/her with a smartwatch free of charge for the study period.
We will then ask him/her to install the study App on your smartphone and to set up the smartwatch using the operating instructions. This will include the installation of the smartphone app.
After each night, the smartphone App will ask whether both of you think that an episode of RBD

has occurred. The person you care for usually does not know whether an episode of RBD occurred during the night, this is why we ask both of you. This is the only information you will need to contribute to the study.
Knowing whether an episode of RBD occurred during the night will make it easier for our data analysts to identify the important pieces of data in the recordings. Based on these recordings, they will then develop an algorithm that can detect RBD just based on the smartwatch data.

After 4 weeks, the smartwatch will be returned to the study centre and the App deinstalled.

Conditions of participation

The doctor will invite the patient to participate in this research and will inform him/her of the objective, the digital processing of data concerning the patient that will be collected during this research and will also specify the patient's rights of access, opposition and rectification to these data.
The doctor will also check the eligibility criteria. If the patient agrees to participate, he/she will orally give his/her consent and his/her non-opposition is documented in his/her medical file. The participant may, at any time, object to the use of his/her data as part of the research.
As the care partner of the patient, you will be informed too and should not be opposed to the patient participation.

Ethical and legal issues

The researchers involved in the study follow the principles described in the latest version of the Declaration of Helsinki. The study was reviewed by the ethics committee of the TU Dresden and approved for implementation.

Risks

No risks are expected by participating in this study.

Data protection

In this study, your personal data noted above will be stored:

(1) Your name and the month and year of birth are recorded in a document termed enrollment log. This is the only place it is stored. It is a paper document stored in a folder in the study centre and only study personnel have access to the folder.
(2) We sill store the information whether you think that an episode of RBD occurred in the person you care for during the previous night. This information will be entered on the smartphone and stored with the code (pseudonym) of the person you care for on a dedicated server. During transfer to the server, the data is encrypted, and it is also stored in encrypted form.

Different partners of the AI-PROGNOSIS project are involved in analysing the information about the RBD episodes. They can only see the code and not your real name. Only people with access to the enrolment log can know whose data it is.

The following partners will receive data and participate in data analysis:

- ARISTOTELEIO PANEPISTIMIO THESSALONIKIS (AUTH), with legal address KEDEA BUILDING, TRITIS SEPTEMVRIOU, ARISTOTLE UNIVERSITY CAMPUS, THESSALONIKI 546 36, Greece
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- KING'S COLLEGE LONDON (KCL), with legal address STRAND, LONDON WC2R 2LS, United Kingdom
- NETCOMPANY-INTRASOFT SA (INTRA), with legal address RUE NICOLAS BOVE 2B, LUXEMBOURG 1253, Luxembourg,
- SQUAREDEV (SQD), with legal address KANTERSTEEN 47, BRUSSELS 1000, Belgium,
- TECHNISCHE UNIVERSITAET DRESDEN (TUD), with legal address HELMHOLTZSTRASSE 10, DRESDEN 01069, Germany,

All participating partners are subject to the European Data Protection Regulation. The legal basis for data processing is your consent (Article 9(2)(a) and Article 6(1)(a) of the European Data Protection Regulation).
The Department of Neurology of the Medical Faculty Carl Gustav Carus Dresden is responsible for processing your patient data. The responsible data protection officer can be reached at:

University Hospital Carl Gustav Carus Dresden, Data Protection Officer
Fetscherstrasse 74
01307 Dresden
E-mail: DSV@uniklinikum-dresden.de

You also have the possibility to file a complaint with any data protection supervisory authority. You have the right to obtain information about the data that is related to you. You have the right to receive your data in a standardised electronic format or to have it transferred to an office named by you (right to data portability).

Contact

If you have any further questions or problems, you can contact the principal investigator at any time:

Prof. Dr. med. Björn Falkenburger
Klinik und Poliklinik für Neurologie
Universitätsklinikum Carl Gustav Carus
an der Technischen Universität Dresden
Fetscherstraße 74
01307 Dresden
Email: bfalken@ukdd.de
Tel: 0351 458 2532

ai·prognosis

Patient information and consent form for the non-interventional observational research study for *" Digital biomarkers development, validation and verification (dBM-DEV) "*

Development cohort: Control participants

Dear participant,

We are asking you whether you would like to participate in our study because you have the same age and sex as a person with REM sleep behaviour disorder (RBD) that participates in our study Digital biomarkers development, validation and verification (dBM-DEV). This study is testing whether RBD can be detected by information recorded by a smartwatch. Please read this patient information carefully and feel free to ask us for further information.

Aim of the study

Neuroprotective treatments will be most useful if administered early in the course of any neurodegenerative disease. Several neurodegenerative diseases, including Parkinson's disease, are preceded by a prodromal phase, a phase of first symptoms announcing the actual illness. This prodromal phase is characterised by specific symptoms, including RBD. People with RBD may scream or kick their feet during sleep, sometimes falling out of bed or hurting people sleeping close to them.
RBD is not a common condition, affecting only one in 100-200 people. And RBD can only be diagnosed with certainty in a sleep lab. In a sleep lab, people need to be in the hospital for one or two nights with wires recording heart rate, blood pressure, movements and brain waves (EEG). This is cumbersome, and not everyone can be admitted to a sleep lab. In order to find people with RBD more easily, a screening tool has been developed. It is called the RBD screening questionnaire (RBDSQ).
Yet, the RBDSQ is not perfect; among 100 people where RBD can be suspected based on the RBDSQ, only 42 will actually have RBD when they undergo investigation in the sleep lab. So the sleep lab investigation will not be necessary for more than half of the people with a positive RBDSQ. In order to improve finding people with RBD, and in order to reduce the number of people undergoing investigation in a sleep lab, we want to use digital biomarkers recorded by a smartwatch. In order to develop these biomarkers, we need to compare movements between people with RBD and people without RBD.

Procedure of the study

This study is conducted in parallel with four other European sites. In each site, 30 participants will be enrolled.
The study will be conducted over a total period of four weeks. If you participate in the study, we will provide you with a smartwatch free of charge for the study period. We will perform an initial assessment, which takes about 30 minutes. Specifically, we will ask you about general information (age, handedness) and conduct the following scales that are standard for patients with PD to

complete:

- Cognitive test (MoCA)
- Screening questionnaire for REM sleep behaviour disorder (RBDSQ)
- Questionnaire about sleepiness (Epworth Sleepiness Scale)
- Standard motor examination (MDS-UPDRS)

We will then ask you to install the study App on your smartphone and to set up the smartwatch using the operating instructions. This will include the installation of the smartphone app. A study supervisor is available to help you here at any time. You can also contact us in case of technical problems at any time during the course of the study.
The smartwatch will record the movements of your arm during sleep, and also other data like blood pressure and heart rate. The information will be transmitted to your smartphone. From the smartphone it will be transmitted to the study cloud whenever your smartphone is connected to a free wireless network.
The data recorded by the smartwatch will be stored on your smartphone and transmitted to the study cloud whenever you have wifi access.
The study team will call you after 2 weeks to ask whether everything works well, and every four weeks after taht.
After 4 weeks, you will return the smartwatch to the study centre and deinstall the App.

Conditions of participation

Your participation in the study is voluntary. Your treatment will not be affected by the study. You confirm your willingness to participate by signing this document, a copy of which will be given to you. You can withdraw your consent to the study at any time without having to give us a reason, and without any further disadvantages for the future treatment of your disease.
You are not expected to benefit directly from your participation in the study. However, you can contribute to finding patients with RBD more easily in the future by participating in this trial.
We cannot offer you any remuneration for your voluntary participation in the study.

Ethical and legal issues

The researchers involved in the study follow the principles described in the latest version of the Declaration of Helsinki. The study was reviewed by the ethics committee of the TU Dresden and approved for implementation.

Risks

No risks are expected by participating in this study.

Data protection

In this study, your personal data will be stored. Your name and the month and year of birth are recorded in a document termed enrollment log. This is the only place. It is a paper document stored in a folder in the study centre and only study personnel have access to the folder. In all other places, your personal data (age, smartwatch data) is only identified by code or pseudonym (e.g. DD1234) from which you cannot be identified.
The smartphone data is stored on a dedicated server together with your pseudonym. During transfer to the server, the data is encrypted, and it is also stored in encrypted form.
Different partners of the AI-PROGNOSIS project are involved in analysing the smartphone data, but

they can only see your code and not your real name. Only people with access to the enrollment log can know whose data it is.
The following partners will receive data and participate in data analysis:

- ARISTOTELEIO PANEPISTIMIO THESSALONIKIS (AUTH), with legal address KEDEA BUILDING, TRITIS SEPTEMVRIOU, ARISTOTLE UNIVERSITY CAMPUS, THESSALONIKI 546 36, Greece
- AINIGMA TECHNOLOGIES (AING), with legal address KAPELDREEF 60, LEUVEN 3001, Belgium,
- CENTRE HOSPITALIER UNIVERSITAIRE DE TOULOUSE (CHUT), with legal address 2 RUE VIGUERIE HOTEL DIEU SAINT JACQUES, TOULOUSE CEDEX 9 31059, France,
- ETHNIKO KENTRO EREVNAS KAI TECHNOLOGIKIS ANAPTYXIS (CERTH), with legal address CHARILAOU THERMI ROAD 6 KM, THERMI THESSALONIKI 57001, Greece,
- FACULDADE DE MOTRICIDADE HUMANA (FMH), with legal address ESTRADA DA COSTA, CRUZ QUEBRADA LISBOA 1495-688, Portugal,
- FUNDACION INICIATIVA PARA LAS NEUROSCIENCIAS - FOUNDATION FOR INITIATIVES IN NEUROSCIENCE (FIN), with legal address CALLE REVENTON 11, MADRID 28002, Spain,
- KATHOLIEKE UNIVERSITEIT LEUVEN (KUL), for the purposes of this agreement represented by KU Leuven Research & Development, with legal address WAAISTRAAT 6 – BOX 5105, LEUVEN 3000, Belgium,
- KING'S COLLEGE LONDON (KCL), with legal address STRAND, LONDON WC2R 2LS, United Kingdom
- NETCOMPANY-INTRASOFT SA (INTRA), with legal address RUE NICOLAS BOVE 2B, LUXEMBOURG 1253, Luxembourg,
- SQUAREDEV (SQD), with legal address KANTERSTEEN 47, BRUSSELS 1000, Belgium,
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The Department of Neurology of the Medical Faculty Carl Gustav Carus Dresden is responsible for processing your patient data. The responsible data protection officer can be reached at:

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You also have the possibility to file a complaint with any data protection supervisory authority. You have the right to obtain information about the data that is related to you. You have the right to receive your data in a standardised electronic format or to have it transferred to an office named by you (right to data portability).

Right to object

Your consent is voluntary!
You can completely revoke your consent to further participation in this study at any time without giving reasons and without any adverse consequences for you. A revocation always refers only to the future use of your patient data. Data from analyses that have already been carried out cannot be subsequently removed.
For a revocation, please contact the principal investigator indicated below under Contact.

Contact

If you have any further questions or problems, you can contact the principal investigator at any time:
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Klinik und Poliklinik für Neurologie
Universitätsklinikum Carl Gustav Carus
an der Technischen Universität Dresden
Fetscherstraße 74
01307 Dresden
Email: bfalken@ukdd.de
Tel: 0351 458 2532

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Informed consent for the research study for

" Digital biomarkers development, validation and verification (dBM-DEV) "

Development cohort: Control participants

I give my consent to participate in the above non-invasive study. I understand that my participation is voluntary. I may withdraw my consent at any time without prior notice and without giving reasons, without any disadvantage to me.

In addition, I declare my consent to the following data protection provisions:

a. I agree that some of the data collected in the study, in particular my gender and age, will be provided by code number only and will be recorded in computers, stored and processed for scientific purposes in the context of the present study.

b. In case of publication of research results, the data will only be used in coded form. No results allow the identification of the person.

c. Anonymised data will be made available to the scientific communing according to the FAIR principles.

I have received the written patient information about the above research project and have been given a copy of my signed consent form to participate.

Yes, I would like to participate in the study.

No, I do not want to take part in the study.

_____

(name of the study participant)

_____

(date & signature study participant)

_____

(name of the investigator)

_____

(signature and stamp of investigator)

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Patient information and consent form for the non-interventional observational research study for *" Digital biomarkers development, validation and verification (dBM-DEV) "*

Confirmation cohort

Dear participant,

Because you have been diagnosed with Parkinson disease, we are asking you whether you would like to participate in our study. This study is testing whether REM sleep behaviour disorder (RBD) can be detected by information recorded by a smartwatch. Please read this patient information carefully and feel free to ask us for further information.

Aim of the study

Neuroprotective treatments will be most useful if administered early in the course of any neurodegenerative disease. Several neurodegenerative diseases, including Parkinson's disease, are preceded by a prodromal phase, a phase of first symptoms announcing the actual illness. This prodromal phase is characterised by specific symptoms, including RBD. As you know people with RBD may scream or kick their feet during sleep, sometimes falling out of bed or hurting people sleeping close to them.

RBD is not a common condition, affecting only one in 100-200 people. And RBD can only be diagnosed with certainty in a sleep lab. In a sleep lab, people need to be in the hospital for one or two nights with wires recording heart rate, blood pressure, movements and brain waves (EEG). This is cumbersome, and not everyone can be admitted to a sleep lab. In order to find people with RBD more easily, a screening tool has been developed. It is called the RBD screening questionnaire (RBDSQ).

Yet, the RBDSQ is not perfect; among 100 people where RBD can be suspected based on the RBDSQ, only 42 will actually have RBD when they undergo investigation in the sleep lab. So, the sleep lab investigation will not be necessary for more than half of the people with a positive RBDSQ. In order to improve finding people with RBD, and in order to reduce the number of people undergoing investigation in a sleep lab, we want to use digital biomarkers recorded by a smartwatch.

Procedure of the study

This study is conducted in parallel with four other European sites. In each site, 30 participants will be enrolled.

The study will be conducted over a total period of four weeks. If you participate in the study, we will first conduct two assessments to see whether you can participate in the study. Both assessments are standard for patients to complete:

- Cognitive test (MoCA)
- Screening questionnaire for REM sleep behaviour disorder (RBDSQ)

These assessments take about 20 min to complete. If you fit into the study population, we will

provide you with a smartwatch free of charge for the study period. We will perform additional assessments, which take about 15 minutes. Specifically, we will ask you about general information (age, year of first symptoms, handedness, …) and conduct the following scales that are standard for patients with PD:

- Questionnaire about sleepiness (Epworth Sleepiness Scale)
- Standard motor examination (MDS-UPDRS)

We will then ask you to install the study App on your smartphone and to set up the smartwatch using the operating instructions. This will include the installation of the smartphone app. A study supervisor is available to help you here at any time. You can also contact us in case of technical problems at any time during the course of the study.
The smartwatch will record the movements of your arm during sleep, and also other data like blood pressure and heart rate. The information will be transmitted to your smartphone. From the smartphone it will be transmitted to the study cloud whenever your smartphone is connected to a free wireless network.
During the course of the study, will ask you to spend one night in the hospital for polysomnography. This is a standard diagnostic test and will be scheduled based on your availabilities and based on vacancies in the sleep lab.
Every two weeks, you will be asked to use your smartphone to record a video (1 min maximum duration) while standing, rising from a chair, walking away from the camera and back, tapping your left and right leg. To preserve your privacy, an avatar will be fitted to each video after acquisition. Only the avatar will be stored and transferred to the study cloud. Video data will not be stored in the study app or transmitted to the study cloud.
Finally, you will be asked to complete three short cognitive tasks every two weeks. They require less than 15 minutes in total.
The data recorded by the smartwatch will be stored on your smartphone and transmitted to the study cloud whenever you have wifi access.
The study team will call you after 2 weeks to ask whether everything works well, and every four weeks after taht.
After 4 weeks, you will return the smartwatch to the study centre and deinstall the App.

Conditions of participation

Your participation in the study is voluntary. Your treatment will not be affected by the study. You confirm your willingness to participate by signing this document, a copy of which will be given to you. You can withdraw your consent to the study at any time without having to give us a reason, and without any further disadvantages for the future treatment of your disease.
You are not expected to benefit directly from your participation in the study. However, you can contribute to finding patients with RBD more easily in the future by participating in this trial.
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Risks

No risks are expected by participating in this study.

Data protection

In this study, your personal data will be stored. Your name and the month and year of birth are recorded in a document termed enrollment log. This is the only place. It is a paper document stored in a folder in the study centre and only study personnel have access to the folder. In all other places, your personal data (age, year of diagnosis, smartwatch data) is only identified by code or pseudonym (e.g. DD1234) from which you cannot be identified.
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Tel: 0351 458 2532

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Informed consent for the research study for

" Digital biomarkers development, validation and verification (dBM-DEV) "

Confirmation cohort

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In addition, I declare my consent to the following data protection provisions:

a. I agree that some of the data collected in the study, in particular my health information, gender and age, will be provided by code number only and will be recorded in computers, stored and processed for scientific purposes in the context of the present study.

b. In case of publication of research results, the data will only be used in coded form. No results allow the identification of the person.

c. Anonymised data will be made available to the scientific communing according to the FAIR principles.

I have received the written patient information about the above research project and have been given a copy of my signed consent form to participate.

Yes, I would like to participate in the study.

No, I do not want to take part in the study.

_____
(name of the study participant)

_____
(date & signature study participant)

_____
(name of the investigator)

_____
(signature and stamp of investigator)

Comité de protection des personnes Ile de France III

Avis sur une demande initiale

CPP

Nom du CPP : Comité de protection des personnes Ile de France III
Adresse : Hôpital TARNIER COCHIN - 89, rue d'Assas 75006 PARIS France
Courriel : cpp.iledefrance3@orange.fr
Téléphone : 0616191639

Promoteur / Demandeur

Promoteur : CHU de TOULOUSE
Représentant légal (UE) : -

Mandataire : -

Dossier

Numéro SI : 23.04654.000511
Numéro national : 2023-A02136-59
Référence interne : RC31/23/0184

Règlementation : Loi Jardé
Qualification : Catégorie 2

Produit ou acte : Hors produits de santé (produits non mentionnés à l'article L.5311-11 du code de la santé publique)
Investigateur : Dr FABBRI

Titre : **Etude dBM-DEV : Développement, validation et vérification de biomarqueurs numériques du trouble du comportement en sommeil paradoxal**

Ce dossier a été étudié en séance le 23/01/2024 et mandat a été donné au président du CPP d'émettre l'avis à réception des réponses du déposant aux dernières demandes. Au vu des réponses obtenues, l'avis suivant a donc été émis. Cet avis court à compter du changement de statut sur le SI.

Considérant que les conditions éthiques sont remplies notamment au regard des éléments de l'article L.1123-7 du code de la santé publique, l'examen du comité permet de conclure que la recherche peut être réalisée et de rendre l'avis suivant :

Avis favorable

Cet avis est valable deux ans. Conformément à l'article L.1123-11 du code de la santé publique, le promoteur doit déclarer au CPP le début de la recherche. Cette déclaration se fait directement sur le SIRIPH2G (bouton "démarrer l'étude").

Si vous n'avez pas été en mesure d'inclure un premier participant à la recherche dans ce délai, vous pouvez demander au CPP une prorogation de cet avis avant la fin de validité de ce dernier (article R.1123-26 du code de la santé publique).

Sur les motivations suivantes :
L'étude apparaît pertinente et le rapport bénéfices/risques acceptable.
La méthodologie est clairement décrite et adaptée aux objectifs.
Les notices d'information et de consentement sont clairement rédigés. Ils contiennent toutes les mentions.

Personnes ayant délibéré

Collège	Catégorie	Nom et prénom	Fonction
Collège I	Qualification RIPH - Biostatistique ou épidémiologie	BIGOT Thierry	
Collège I	Qualification RIPH - Biostatistique ou épidémiologie	DHOTE Robin	
Collège I	Qualification RIPH - Autre	CHRISTOFOROV Boyan	
Collège I	Qualification RIPH - Autre	LOULERGUE Pierre	Président
Collège I	Qualification RIPH - Autre	AMADOR Maria del Mar	
Collège I	Pharmacien hospitalier	PARISCOAT Guillaume	
Collège I	Auxiliaire médical	BONVALLET Bérangère	
Collège II	Compétence éthique	POLETTO-FORGET Cristina	
Collège II	Compétence éthique	DRAPEAU Julie	
Collège II	Compétence en sciences humaines et sociales ou action sociale	BESLE Sylvain	
Collège II	Compétence en sciences humaines et sociales ou action sociale	CAMUS Catherine	
Collège II	Compétence en sciences humaines et sociales ou action sociale	OLMOS Adjouani	
Collège II	Compétence juridique	SIMHON David	Vice-président
Collège II	Représentant d'association agréée	MORIN Paulette	
Collège II	Représentant d'association agréée	LAMARCHE Dominique	

Documents analysés par le CPP

Catégorie	Intitulé	Date de dépôt
ADD - Doc additionnel	*2023-A02136-59 DOCUMENT ADDITIONNEL DbM-DEV V1.0 du 19122023.pdf*	21/12/2023
ASS - Assurance	*2023-A022136-59 Assurance dBM-DEV.pdf*	21/12/2023
COU - Courrier	*2023-A02136-59 -Courrier Demande-V1.0 19122023 - DBM-DEV.pdf*	21/12/2023
CVI - CV investigateurs	*CV _Fabbri M Déc 2023.pdf*	21/12/2023
CVI - CV investigateurs	*CV PR RASCOL 2023.pdf*	21/12/2023
CVI - CV investigateurs	*Attestation BP Pr Rascol 2022.pdf*	21/12/2023
CVI - CV investigateurs	*BPC_MFABBRI MAI 2022 (1).pdf*	21/12/2023
DEM - Demande autorisation	*2023-A02136-59 HPS-Form-Demande-Initiale-AEC -etude dBM-DEV.pdf*	21/12/2023
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV aidant patients MP V1.0 19122023.pdf*	21/12/2023
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV aidant patients TCSP V1.0 19122023.pdf*	21/12/2023
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV controle V1.0 19122023.pdf*	21/12/2023
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV patients MP V1.0 19122023.pdf*	21/12/2023
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV patients TCSP V1.0 19122023.pdf*	21/12/2023
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV controle V1.1 02022024.docx*	02/02/2024

INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV aidant patients TCSP V1.1 02022024.docx*	02/02/2024
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV aidant patients MP V1.1 02022024.docx*	02/02/2024
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV patients TCSP V1.1 02022024.docx*	02/02/2024
INF - Doc Information	*2023-A02136-59 NIFC_dBM-DEV patients MP V1.1 02022024.docx*	02/02/2024
JUS - Justification lieux de recherche	*2023-A02136-59 Justification adequation.pdf*	21/12/2023
LET - Lettre	*Réponses au CPP.docx*	02/02/2024
LIS - Liste investigateurs	*2023-A02136-59 Liste investigateurs_dBM-DEV V1.0 19122023.pdf*	21/12/2023
PRO - Protocole	*2023-A02136-59 Protocol v1.0 19122023 dBM-DEV.pdf*	21/12/2023
QUE - Echelles/questionnaires	*2023-A02136-59 questionnaire UPDRS_French_Official_Translation_FINAL.pdf*	21/12/2023
RES - Résumé	*2023-A02136-59 Résumé_dBM-DEV V1.0 19122023.pdf*	21/12/2023

**Les documents étiquetés non-conformes sur le SI RIPH2G ou transmis pour information/notification dans le cadre de cette demande d'avis n'ont pas été évalués par le CPP.*
**L'intitulé des documents examinés par le comité, listés sur le présent avis, reprend la nomenclature des fichiers utilisée par le déposant sur le SI RIPH2G.*

Le 06 Février 2024
Le Président : Pierre LOULERGUE

Sa-18773 / 15 - EC: 535

DICTAMEN FAVORABLE. CERTIFICADO ACEPTACIÓN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

D. José Domingo García Labajo, Secretario del **Comité de Ética de la Investigación con medicamentos del Hospital Ruber Internacional de Madrid.**

CERTIFICA

Que este Comité ha evaluado la siguiente propuesta de ensayo clínico

EudraCT:	Codigo: **Estudio dBM-DEV**
Titulo:	***Estudio de desarrollo, validación y verificación de biomarcadores digitales (Estudio Dbm-DEV)*** ***AI-prognosis digital biomarkers development study (dBM-DEV study)***
Promotor:	**AI Prognosis**
C.R.O.:	Monica Kurtis Mª Luisa ALMARSA

Identificación de la modificación

Enmienda	Presentación Inicial:
Relación de Documentos Modificado (Versión; Fecha)	
Protocolo	➢ **Protocolo** (En- 18735 /2-535; 4/5/2024) Protocolo Version 1.2 de 01 APR 2024
Hoja de Información	➢ **Hoja Información** (En- 18736 /3-535; 4/5/2024) Información para el paciente y formulario de consentimiento para el estudio de investigación observacional no intervencionista para "Desarrollo, validación y verificación de biomarcadores digitales (dBM-DEV)". Cohorte de confirmación. ➢ **Hoja Información** (En- 18737 /3-535; 4/5/2024) Información para el paciente y formulario de consentimiento para Cohorte de desarrollo: participantes de control. Información para el paciente y formulario de consentimiento para el estudio de investigación observacional no intervencionista para "Desarrollo, validación y verificación de biomarcadores digitales (dBM-DEV)". Cohorte de desarrollo: participantes de control. ➢ **Hoja Información** (En- 18738 /3-535; 4/5/2024) Información para el paciente y formulario de consentimiento informado para Cohorte de desarrollo: Participantes con trastorno de conducta delsueño REM. Información para el paciente y formulario de consentimiento informado para el estudio de investigación observacional no intervencionista "Desarrollo, validación y verificación de biomarcadores digitales (dBM-DEV)". Cohorte de desarrollo: Participantes con trastorno de conducta del sueño REM. ➢ **Hoja Información** (En- 18739 /3-535; 4/5/2024) Folleto informativo "Desarrollo, validación y verificación de biomarcadores digitales (dBM-DEV)" Cohorte de desarrollo: cuidador principal.

Que este Comité ha realizado la evaluación de la solicitud de aceptación del estudio y ha valorado las respuestas del promotor a las aclaraciones solicitadas y considera que:

El proyecto respeta los principios fundamentales expuestos en la declaración de Helsinki de 1964 de la Organización Médica Mundial y sus versiones posteriores y los del Convenio del Consejo de Europa de 1996 relativos a los Derechos Humanos y la Investigación Biomédica, cumpliendo los requisitos de la normativa legal que pudiera afectarle y su realización es pertinente.

La capacidad del investigador y sus colaboradores, y las instalaciones y medios disponibles, tal y como ha sido informado, son apropiados para llevar a cabo el estudio; habiendo demostrado los autores conocer suficientemente los antecedentes y el estado actual del tema que proponen investigar.

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio; la metodología propuesta es adecuada y están justificados los riesgos y molestias previsibles para los participantes, teniendo en cuenta los beneficios esperados.

Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.

El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Por lo que se hace constar la viabilidad y procedencia en todos sus términos del proyecto de investigación, estimando que los resultados alcanzados pueden ser de gran interés.

Este CEIm acepta que dicho estudio sea realizado en nuestro Hospital por la Dra "**Monica Kurtis"** y sus investigadores colaboradores.

Que este Comité decidió emitir **DICTAMEN FAVORABLE** en la reunión celebrada el día 08 de Abril de 2024 (Acta nº 260)

Que en dicha reunión se cumplieron los requisitos establecidos en la legislación vigente – Real Decreto 1090/2015 – para que la decisión del citado CEIm sea válida.

Que el CEIm del Hospital Ruber Internacional, tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm es la indicada en el anexo I, teniendo en cuenta que en el caso de que algún miembro participe en el ensayo o declare algún conflicto de interés no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del ensayo clínico.

Fdo. José Domingo GARCÍA LABAJO

Secretario del CEIm

GARCIA LABAJO JOSE DOMINGO - 50405817Y

Firmado digitalmente por GARCIA LABAJO JOSE DOMINGO - 50405817Y
Fecha: 2024.04.29 20:58:09 +02'00'

Dictamen. Certificado de Aceptación.

Anexo I. Composición Actual del CEIm.

Composición del CEIm Hospital Ruber Internacional de Madrid	
Presidente	Dra. Dña. Mercedes CUESTA NUIN (Directora Médico)
Vicepresidente	Dra. Dña. Mª del Mar GARCÍA ARENILLAS (Farmacólogo Clínico) Ajeno a H.R.I.
Vocales	Dr. D. Régulo José AVILA MARTÍNEZ (Cirugía Torácica)
	Dra. Dña. Aurora RODRÍGUEZ PÉREZ (Oncología Radioterápica).
	Dra. Dña. Mª Ángeles SANZ DONOSO (Pediatria. Máster en Bioética).
	Dra. DÑA. Carmen A. HARO MARQUEZ (Farmacia Hospitalaria).
	D. Carlos PADILLA MÉNDEZ (Lego en Ciencias de La Salud – Representante de los Pacientes) Ajeno a H.R.I.
	D. Isidro DÍAZ DE BUSTAMANTE Y TERMINEL (Doctor en Derecho). Ajeno a H.R.I.
	Dña Susana MONTENEGRO MÉNDEZ (Enfermera Supervisora de Medicina Intensiva).
	Dr. D. Jesús ESTEBAN PÉREZ (Neurología)
	Dra. Dña. Jimena RAMÓN GARCIA (Farmacéutica de Atención Primaria) Ajena a H.R.I:
Secretario técnico	Dr. D. José Domingo GARCÍA LABAJO

Dictamen. Certificado de Aceptación.

Anexo II – Listado de Centros Participantes

IDENTIFICACIÓN DE LA SOLICITUD

EudraCT:		Codigo: **Estudio dBM-DEV**
Titulo:	***Estudio de desarrollo, validación y verificación de biomarcadores digitales (Estudio Dbm-DEV)*** ***AI-prognosis digital biomarkers development study (dBM-DEV study)***	
Promotor:	**AI Prognosis**	
C.R.O.:	Monica Kurtis Mª Luisa ALMARSA	
Modificación Sustancial Enmienda		Presentación Inicial
Fecha Actualización Anexo II		08 Abril 2024

Listado de Investigadores Principales y Centros Participantes Autorizados en España

Investigador	Centro
1. Monica Kurtis	• Hospital Ruber Internacional.
2. Maria Luisa Almarcha Menargues	• Hospital Ruber Internacional.

TECHNISCHE UNIVERSITÄT DRESDEN

Ethikkommission

Ethikkommission an der TU Dresden
Fetscherstraße 74, 01307 Dresden

Herrn
Prof. Dr. med. Björn Falkenburger
Klinik und Poliklinik für Neurologie
Universitätsklinikum Carl Gustav Carus Dresden
-Hauspost-

Prof. Dr. med.
Bertold Renner
Vorsitzender der Ethikkommission

Telefon: 0351 458-2992
Telefax: 0351 458-4369
E-Mail: ethikkommission@mailbox.tu-dresden.de

Dresden, 31.05.2024

Auflagenerfüllung

Studie: AI-prognosis digital biomarkers development study (dBM-DEV study)

unser AZ: BO-EK-2012024 *(bitte stets angeben!)*

eingereicht von: Prof. Dr. med. Björn Falkenburger – Klinik und Poliklinik für Neurologie

Sehr geehrter Prof. Dr. med. Björn Falkenburger,

mit den ergänzenden Unterlagen zu o. g. Studie, die am 24.04.2024 hier eingegangen sind, wurden die Auflagen aus unserem Schreiben vom 11.03.2024 erfüllt.

Nach Auffassung der Ethikkommission an der Technischen Universität Dresden bestehen nunmehr gegen das Forschungsvorhaben

☒ keine Bedenken.

☐ keine Bedenken. Die im Einzelnen aufgeführten weiteren Hinweise bzw. Empfehlungen[1] sollten jedoch berücksichtigt werden. Eine erneute Vorlage der überarbeiteten Unterlagen ist nicht notwendig.

[1] *Hinweise und Empfehlungen sollen auf die moralische und juristische Verpflichtung hinweisen und in freier Entscheidung und Verantwortung zur Überprüfung und Anpassung der Studiendokumente anregen.*

Die allgemeinen Hinweise aus der mit Auflagen versehenen Erstberatung gelten entsprechend und sind zu berücksichtigen.

Die Ethikkommission an der TU Dresden stützt sich bei der Beurteilung der eingereichten Studienunterlagen insbesondere auf die Richtlinien der Deklaration des Weltärztebundes von Helsinki in der jeweils geltenden Fassung, auf die strahlenschutzrechtlichen Vorschriften und auf die allgemein anerkannten Richtlinien für „Good Clinical Practice" (GCP).

Die Arbeitsweise und die Zusammensetzung der Ethikkommission entspricht den jeweils geltenden gesetzlichen Regelungen bzw. Empfehlungen.

Es wird bestätigt, dass keine Mitglieder der Ethikkommission, die am o. g. Forschungsvorhaben beteiligt sind, am Beratungs- bzw. Bewertungsergebnis mitgewirkt haben oder in anderer Form beteiligt gewesen sind.

Wir wünschen Ihnen bei der Durchführung Ihres Forschungsvorhabens viel Erfolg.

Mit freundlichen Grüßen

Carl Bertold Renner

Digital signiert von Carl Bertold Renner
DN: cn=Carl Bertold Renner, c=DE, o=Technische Universitaet Dresden, email=bertold.renner@tu-dresden.de
Datum: 2024.06.03 22:26:51 +02'00'

Prof. Dr. med. B. Renner
Vorsitzender der Ethikkommission

AI-PROGNOSIS - Digital Biomarkers Development Study (dBM-DEV) (dBM-DEV)

ClinicalTrials.gov Identifier: NCT06444789

Recruitment Status : Not yet recruiting
First Posted : June 6, 2024
Last Update Posted : June 7, 2024

See **Contacts and Locations**

Sponsor:
University Hospital, Toulouse

Collaborators:
European Union
University Hospital Carl Gustav Carus

Aristotle University Of Thessaloniki

Information provided by (Responsible Party):
University Hospital, Toulouse

Study Description

Go to

Brief Summary:

dBM-dev study is a multicentre low-intervention research study which concerns REM sleep behaviour disorder (RBD) who is the best predictor for neurodegenerative diseases including Parkinson's disease (PD). RBD can only be confirmed by polysomnography, which is a cumbersome procedure. The main objective of this study is to identify a novel, robust dBM for the detection of RBD using smartwatch-based recordings of passive data.The study is conducted step-wise on two subsequent cohorts referred to as the development cohort and the confirmation cohort.

Condition or disease	Intervention/treatment
Parkinson Disease	Device: connected smartwatch

Detailed Description:

The development cohort comprises 30 patients with RBD and 30 matched controls on sex and age with patients RBD.

The confirmation cohort comprises 30 patients with PD. Following a baseline visit comprising standard clinical evaluation and Parkinson questionnaires, participants will undergo daily-life dBM tracking over a duration of 4 weeks for development cohort and 3 months for confirmation cohort. Additionally, PD patients enrolled in the confirmation cohort will receive a polysomnography which permits to verificate if they have a RBD. The investigation is conducted in four European sites.

Study Design

Go to

Study Type :	Observational
Estimated Enrollment :	90 participants
Observational Model:	Case-Control
Time Perspective:	Prospective

Official Title: AI-based Parkinson's Disease Risk Assessment and Prognosis - Digital Biomarkers Development, Validation and Verification Study (AI-PROGNOSIS dBM-DEV Study)

Estimated Study Start Date : July 15, 2024
Estimated Primary Completion Date : July 15, 2025
Estimated Study Completion Date : July 15, 2025

Resource links provided by the National Library of Medicine

MedlinePlus Genetics related topics: Parkinson disease

MedlinePlus related topics: Parkinson's Disease

U.S. FDA Resources

Groups and Cohorts

Go to

Group/Cohort	Intervention/treatment
Development cohort of patients with known RBD Detection of RBD signs by using the connected smartwach during 4 weeks	Device: connected smartwatch The smartwatch is worn by the patient and data are sent automatically to a server that detects if there are signs of RBD.
Development cohort of matched controls = people who don't have RBD age and sex matched Detection of RBD signs by using the connected smartwach during 4 weeks	Device: connected smartwatch The smartwatch is worn by the patient and data are sent automatically to a server that detects if there are signs of RBD.
Confirmation cohort of parkinson disease patients = people who are supposed to have RBD Detection of RBD signs by using the connected smartwach during 3 months	Device: connected smartwatch The smartwatch is worn by the patient and data are sent automatically to a server that detects if there are signs of RBD.

Outcome Measures

Go to

Primary Outcome Measures :

1. Incidence of nights in a confirmation cohort in which RBD episodes are indicated by a score (digital biomarker) derived from passive actigraphy and photoplethysmography data captured by a smartwatch [Time Frame: 4 weeks]

   the digital biomarker will be identified from passive actigraphy and photoplethysmography data of a separate development cohort

Secondary Outcome Measures :

1. correlation between a) and b) [Time Frame: 4 weeks for a) 3 months for b)]
   a. the incidence of daytime somnolence episodes per week indicated by a score (digital biomarker) derived from passive actigraphy and photoplethysmography data captured by a smartwatch. The digital biomarker will be identified from passive actigraphy and photoplethysmography data of a separate development cohort
   b. the score of the Epworth Sleepiness Scale at baseline, measured by the Spearman correlation coefficient, in a confirmation cohort
2. Number of camera-based movement assessments acquired by each participant relative to the number of scheduled camera-based movement assessments. [Time Frame: 4 weeks (for development cohort) and 3 months (for confirmation cohort)]
3. Number of cognitive tasks completed by each participant relative to the number of scheduled cognitive tasks. [Time Frame: 4 weeks (for development cohort) and 3 months (for confirmation cohort)]

Eligibility Criteria

Go to

Information from the National Library of Medicine NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a

study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes
Sampling Method:	Non-Probability Sample

Study Population

1 group of persons with RBD

1 group of persons without RBD

1 group of persons with Parkinson disease

Criteria

Inclusion Criteria for development cohort:

Group of RBD patients

- Diagnosis of RBD (confirmed by polysomnography)
- Able to use a compatible smartphone with the study app
- Having a care partner with whom they share their bedroom at night

Group of Healthy matched controls:

- Healthy volunteers age and sex matched to the enrolled RBD patients.
- Able to use a compatible smartphone with the study app
- No history of RBD.

Inclusion Criteria for confirmation cohort

- Clinical confirmed diagnosis of PD
- RBD Screening Questionnaire score : 3 - 12 points
- Absence of dementia
- Able to use a compatible smartphone with the study app
- Having a care partner with whom they share their bedroom at night

Exclusion Criteria for all cohorts:

Inability to consent for study procedures as judged by the investigator. Lacking motivation to

participate in study procedures as judged by the investigator.

Lack of social security.

Contacts and Locations

Go to

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT06444789***

Contacts

Contact: Nadege ALGANS 33-561777204 algans.n@chu-toulouse.fr

Contact: Anna RIBYCKA 33-561778252 ribycka.a@chu-toulouse.fr

Locations

France

Neurology Toulouse Hospital

Toulouse, France

Contact: Amel DRIF amel.drif@inserm.fr

Principal Investigator: Margherita FABBRI

Sub-Investigator: Olivier RASCOL

Germany

Klinik und Poliklinik für Neurologie of University Hospital (Regulatory autorization pending)

Dresden, Germany

Contact: Björn FALKENBURGER

Principal Investigator: Björn FALKENBURGER

Spain

Hospital Ruber Internacional

Madrid, Spain
Contact: Monica KURTIS

Principal Investigator: Monica KURTIS

United Kingdom

King's college of London (Regulatory authorization pending)
London, United Kingdom
Contact: Dhaval TRIVEDI
Principal Investigator: Dhaval TRIVEDI

Sponsors and Collaborators

University Hospital, Toulouse

European Union

University Hospital Carl Gustav Carus

Aristotle University Of Thessaloniki

Investigators

Principal Investigator:	Margherita FABBRI	Toulouse Hospital
Study Chair:	Björn FALKENBURGER	University Hospital Carl Gustav Carus of Dresde

More Information

Go to

Additional Information:

Related Info EXIT

Responsible Party:	University Hospital, Toulouse
ClinicalTrials.gov Identifier:	NCT06444789 History of Changes
Other Study ID Numbers:	RC31/23/0184 - RC31/24/0031
First Posted:	June 6, 2024 Key Record Dates
Last Update Posted:	June 7, 2024
Last Verified:	June 2024

Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No

Keywords provided by University Hospital, Toulouse:

REM sleep behaviour disorder

Additional relevant MeSH terms:

Parkinson Disease
Parkinsonian Disorders
Basal Ganglia Diseases
Brain Diseases
Central Nervous System Diseases
Nervous System Diseases
Movement Disorders
Synucleinopathies
Neurodegenerative Diseases