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CTC-A No.	19-050
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Monitoring	
Status, Version, Date	V2.0, 16.12.2021

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1. SPONSOR INFORMATION

The regulatory sponsor is the Sponsor-Investigator listed on the cover page of the protocol.

2. LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AE	adverse event
BMI	body mass index
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CRF	case report form
CSF	cerebrospinal fluid
DAT	dopamine transporter
EDC	electronic data capture
EEG	Electroencephalography
FDG	fluorodeoxyglucose
GDS	Geriatric Depression Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
MAH	Marketing Authorisation Holder
MCI	mild cognitive impairment
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NIA-AA	National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association (AA)
NSAE	non-serious adverse event
PET	positron emission tomography
PHI	protected health information
RDC	remote data capture
SAE	serious adverse event
SAP	statistical analysis plan
SCI	subjective cognitive impairment
SUSAR	suspected unexpected serious adverse reactions
TIA	transient ischemic attack

3. SYNOPSIS

Item	**Description**
Protocol Title:	German Dementia Registry
CTC-A No.	19-050
Version Number:	2.0
Regulations	The implementation of this project is subject to § 15 of the medical professional code for doctors in North Rhine Westphalia (BOÄ NRW). The project will be carried out in accordance to the Declaration of Helsinki and the Declaration of Taipeh, ICH E6 Guideline for Good Clinical Practice (GCP), Local Rules, regulations and applicable requirements.
Registry Indication:	SCI, MCI or early dementia of different etiology with biomarkers
Rationale:	Currently, there is no existing biomarker-based registry for cognitive impairment and early dementia in Germany. The data collected will provide prospective and longitudinal data demonstrating the natural course of disease and the current diagnostic and treatment behavior in clinical routine in the German healthcare system.
Objectives:	To create a registry to collecting longterm data on patients with cognitive impairment and early dementia and the impact of treatments.
Design:	Open-ended Registry
Location and Number of Sites:	All centers treating patients with cognitive impairment and early dementia in Germany are invited to participate in this registry.

Number of Planned Subjects:	The German Dementia Registry is an open-ended prospective registry. Patients will be asked to participate in as many annual visits as possible. It is planned to enroll all subjects fulfilling the enrolment criteria and showing up in the daily routine of participating centers during the observational period. It is expected to recruit about 1,000 patients per year. The first recruitment period will last for two years followed by annual follow-up evaluations with open-end. Depending on financial resources recruitment of new patients will be continued after the first two years.
Study Population:	This registry will be conducted in adult patients with a diagnosis of SCI, MCI or early dementia of different etiology (i.e. Alzheimer's Disease, Frontotemporal Dementia, Parkinson's Disease, Lewy-Body Dementia, Progressive Supranuclear Palsy, Corticobasal Degeneration, Normal Pressure Hydrocephalus, Major Depression, Vascular Dementia, Prion-Associated Dementia) and existing fluid and/or imaging biomarkers. Detailed criteria are described in the protocol.

Inclusion criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria.

1. Ability of the participant and/or his/her legally authorized representative (e.g., , spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the register and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local privacy regulations.
2. Participating patients must have a diagnosis of SCI, MCI or early dementia of different etiology (i.e. Alzheimer's Disease, Frontotemporal Dementia, Parkinson's Disease, Lewy-Body Dementia, Progressive Supranuclear Palsy, Corticobasal Degeneration, Normal Pressure Hydrocephalus, Major Depression; Vascular Dementia; Prion-Associated Dementia) with fluid and/or imaging biomarkers.
3. At least 18 years of age.

Inclusion Criteria for Life partner or Caregiver

1. At least 18 years of age.
2. Ability of the participant, as appropriate and applicable, to understand the purpose and risks of the register

Exclusion criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist.

1. Unable or unwilling to provide informed consent.
2. Patients with other diagnoses as mentioned in the inclusion criteria.
3. No available biomarkers such as cerebrospinal fluids (CSF) amyloid beta 1-42, amyloid beta 1-40, amyloid beta 1-42/amyloid beta 1-40 ratio, total tau and phospho-tau, amyloid or tau imaging.

Inclusion Criteria for Life partner

1. Unable or unwilling to provide informed consent.

4. SCHEDULE OF EVENTS

Assessments and schedules are listed below. As this is a registry, variations from this schedule will not be considered deviations. Data (patient characteristics, anamnestic parameter, medication, neurophysiological tests) will be collected during clinical routine procedures. Additional diagnostic parameters (biomarker, imaging, laboratory parameter) will be documented as conducted in clinical routine. Details of further clinical study procedures can be found in the data dictionary (Supplement). The study procedures shall be performed on an annual basis.

Table 1: Overview of assessments during the observation period

Type of visit/Information to collect/Scale/Instrument	Time (min)
Baseline Visit	
Consent, General information, demographic and clinical information	30
Baseline & Follow-Up Visits	
Cognitive Screening (MMSE; MoCA)	10 – 25
Structural and functional imaging information (MR, PET)	10
Blood & CSF biomarkers, APOE, Genetics	10
Functional assessments	
Clinical Dementia Rating Scale (CDR), if full version is not available, clinical impression only	60 or 5
ADCS-ADL-MCI	20
Cognitive assessments	
ADAS-Cog13	30
CERAD-Plus	30
Neuropsychiatric symptoms assessments	
Geriatric Depression Scale – 30 Items (GDS)	10
Neuropsychiatric Inventory (NPI-10)	20
PROMs	
QoL-AD	20
Zarit Burden Interview	15
Modified Perceived Deficits Questionnaire (MPDQ20)	10
Resource Utilization in Dementia - Lite Version (RUD-Lite)	30
Short Form (36) Health Survey (SF-36)	20

Core Visit	Extended Visit	Optional Visit
ca. 90 min	ca. 130 min	ca. 115

5. INTRODUCTION

5.1. Background

Dementia is a multifactorial disease that constitutes a challenge both for diagnosis and treatment. The most common cause of dementia is Alzheimer's disease (AD), accounting for 50% to 75% of all cases. In 2019, 50 million people were affected worldwide. Driven by population ageing, this number is expected to increase to 152 million by 2050 [Alzheimer's Disease International 2019].

Clinically, AD is a progressive neurodegenerative disorder characterized by an insidious and unrelenting decline in cognition and behavioral disturbances that result in the person's inability to perform usual activities of daily living [Jack et al. 2013].

Pathologically, AD is defined by the presence of extracellular neuritic plaques containing Aβ peptide and intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau proteins in the brain. The pathogenesis of these plaques and tangles and how they contribute to the clinical syndrome still remain to be fully elucidated. Currently, the leading hypothesis – the "amyloid cascade" – proposes that accumulation of Aβ resulting from an imbalance between Aβ production and Aβ clearance in the brain is the driving force causing the disease [Hardy and Selkoe 2002].

Biomarker [Jack et al. 2010], clinicopathological [Delacourte et al. 2002], and cohort [Amieva et al. 2008] studies suggest that the disease process commences 10 to 20 years prior to the onset of symptoms, starting with the deposition of neocortical Aβ plaques and mesial temporal tau-containing NFTs followed years later by neocortical tau-containing NFTs, which best correlate with cognitive status and neuronal death [Nelson et al. 2009]. As the disease progresses, cognitive impairments, behavioral changes, and functional disability manifest [Jack et al. 2013]. Thus, it is hypothesized that removal of Aβ plaques and subsequent alteration of tau pathology may slow cognitive decline.

Based on the assumption of an early pathological onset decades before symptom onset, the scientific community has focused on developing treatments for patients in earlier stages of the AD continuum. This shift in focus was made possible in part by the development of diagnostic criteria for the diagnosis of earlier stages of Alzheimer's disease in clinical research studies published by the National Institute on Aging at National Institutes of Health and the Alzheimer's Association (NIA-AA) [Albert et al. 2011, McKhann et al. 2011, Sperling et al. 2011] and by an International Working Group (IWG) [Dubois et al. 2010]. These criteria address the need to define the clinical diagnosis of the predementia phases of Alzheimer's disease (e.g., mild cognitive impairment due to AD) and to improve diagnostic specificity by incorporating biomarkers of Alzheimer's disease pathology into the diagnostic process. In 2014, IWG criteria were updated (IWG-2) [Dubois et al. 2014]. The improved diagnostic framework, combined with the ability to confirm underlying disease pathology by using CSF biomarkers or Aβ PET, enabled more accurate diagnosis of AD in predementia subjects. Most recently, in 2018, the NIA-AA Research Framework for AD has further evolved the thinking on diagnosis of AD, recommending that AD is defined by its underlying pathologic processes that can be documented by postmortem examination or *in vivo* by biomarkers [Jack et al. 2018], supporting the use of certain imaging and CSF biomarkers as valid proxies for neuropathologic changes of AD. Amyloid positron emission tomography (PET) is a valid *in vivo* surrogate for Aβ deposits (in brain parenchyma/vessel walls) [Jack et al. 2018]. It is also now widely accepted that CSF Aβ42 (or the Aβ42/ Aβ40 ratio) is a valid indicator of an abnormal pathologic state associated with cerebral Aβ [Blennow et al. 2015]. An additional development has been the introduction of PET ligands for pathologic tau [Chien et al. 2013, Villemagne et al. 2014, Villemagne et al. 2015]. By contrast, additional research has highlighted the fact that measures of neurodegeneration or neuronal injury that are commonly used in AD research – magnetic resonance imaging (MRI), fluoro-deoxyglucose (FDG) PET, and CSF total tau (T-tau) – are not specific for AD but rather nonspecific indicators of damage that may derive from a variety of etiologies, for example, cerebrovascular injury [Wirth et al. 2013].

5.2. Rationale

Diagnostic criteria of AD changed over the last decade due to advances in the understanding of the underlying disease process. Since the publication of the NIA-AA guidelines in 2011, there is accumulating evidence indicating that the cognitive decline in AD occurs continuously over a long period, and that progression of abnormal biomarker values is also a continuous process that begins before symptoms [Jack et al. 2018]. Furthermore, certain imaging and CSF biomarkers are now regarded as valid proxies for neuropathologic changes of AD [Jack et al. 2018Jack et al. 2018].

A systematical data capture is crucial to characterize a broad spectrum of patients over an extended period of time through anamnestic, clinical, neurophysiological, biomarker and imaging parameters. Systems are required to monitor treated and untreated dementia patients in a real-life environment to optimize treatment and care. However, currently, there is no existing disease registry for cognitive impairment and dementia in Germany.

The aim of the German Dementia Registry is to prospectively collect longitudinal real-world data on all consenting patients diagnosed in clinical routine with SCI, MCI, and early dementia of different etiologies in Germany, independent of their actual treatment regimen. For this purpose an online platform will be provided. Data are collected during patient visits and items for data collection are aligned with diagnostic/treatment guidelines and clinical procedures. The disease-specific registry will be conducted to prospectively follow the natural course of dementia and to differentiate e.g. patients with Alzheimer's dementia from patients with dementia of other etiology. The data collected will provide prospective and longitudinal data demonstrating the natural course of disease and the current diagnostic and treatment behavior in clinical routine in the German healthcare system. Prospective monitoring of dementia patients is expected to lead to a better understanding of the natural history of dementia and the changes in biomarker values within different etiologies of dementia. This can help to improve and adapt the early diagnostic criteria regarding biomarkers.

6. STUDY OBJECTIVES AND OUTCOMES

6.1. Objectives and Outcomes

The primary objective is the development of a registry to collect longitudinal data on patients with cognitive impairment and early dementia with fluid and/or imaging biomarkers in Germany.

This will allow to evaluate the current diagnostic and treatment behavior and assess the natural history of a cohort of patients with SCI, MCI and early dementia with fluid and/or imaging biomarkers.

The data collected on biomarkers and risk factors will help to differentiate e.g. patients with Alzheimer's dementia from patients with dementia of other etiology and to optimize diagnosis, management and care in a real-life environment.

7. STUDY DESIGN

7.1. Study Overview

This is an open-ended prospective longitudinal multicenter registry in adult patients with SCI, MCI or early dementia of different etiology with fluid and/or imaging biomarkers. All centers that care for patients with cognitive impairments and early dementia are invited to participate in this national register. The goal is to enroll as many patients as possible in German sites and follow them for an extended period of time. Patients will be characterized through anamnestic, patient-reported outcome measures (PROMS), clinical, neuropsychological, neurophysiological, biomarker and imaging parameters. In addition, the participants' life partners are asked to answer questionnaires about their partner's health status. As a disease-specific project, the registry will provide a platform for prospective collection of longitudinal data on German patients with cognitive impairment and early dementia, diagnosed in clinical routine who consent to this process in Germany.

7.2. Overall Study Duration and Follow-Up

The register period will consist of identification and enrollment of patients meeting the eligibility criteria, a baseline visit and annual follow-up visits (± 2 months)

The participant can decide whether to participate in one of the following groups:

1. core visit (90 minutes per visit)

2. core visit + extended visit (115 minutes per visit)

3. core visit + extended visit + optional visit (135 minutes per visit). Patients will be asked to participate in as many annual study visits as possible. The end of study is defined as final collection of data.

7.3. Early Termination of Study

The Sponsor-Investigator may terminate this study at any time.

8. STUDY POPULATION

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria.

4. Ability of the participant and/or his/her legally authorized representative (e.g., , spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the register and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local privacy regulations.
5. Participating patients must have a diagnosis of SCI, MCI or early dementia of different etiology (i.e. Alzheimer's Disease, Frontotemporal Dementia, Parkinson's Disease, Lewy-Body Dementia, Progressive Supranuclear Palsy, Corticobasal Degeneration, Normal Pressure Hydrocephalus, Major Depression; Vascular Dementia; Prion-Associated Dementia) with fluid and/or imaging biomarkers.
6. At least 18 years of age.

Inclusion Criteria for Life partner or Caregiver

3. At least 18 years of age.
4. Ability of the participant, as appropriate and applicable, to understand the purpose and risks of the register

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist.

4. Unable or unwilling to provide informed consent.
5. Patients with other diagnoses as mentioned in the inclusion criteria.
6. No available biomarkers such as cerebrospinal fluids (CSF) amyloid beta 1-42, amyloid beta 1-40, amyloid beta 1-42/amyloid beta 1-40 ratio, total tau and phospho-tau, amyloid or tau imaging.

Inclusion Criteria for Life partner

2. Unable or unwilling to provide informed consent.

9. STUDY PROCEDURES

Once the investigational site has been activated for study participation, patients may be enrolled if they have met the inclusion criteria in Section 8.1 and have not been excluded based on the exclusion criteria in Section 8.2.

To avoid selection bias, investigators are asked to include all patients fulfilling the inclusion criteria in a consecutive way independent on their treatment regimen.

9.1. Enrollment and Registration of Patients

At the time of consent, the patient will be enrolled into the registry.

Patients will be registered at the Screening visit after the Investigator has verified that they are eligible per criteria in Sections 8.1 and 8.2.

9.1.1. Baseline documentation

After enrolment and registration of patients, the Investigator will document as available

- Record demographic data
- Document diagnosis, stage and onset of disease
- Perform and document MMSE, GDS and neuropsychological testing (CERAD-Plus)
- Document fluid (CSF, blood of available) neurodegeneration markers
- Record blood pressure
- Document height and weight
- Document medical history, including co-morbidities and risk factors
- Record AD-specific and any other medication
- Document brain MRI
- Document FDG, amyloid and/or tau PET or DAT-Scan imaging, if available
- Collect material to the cBMB
- Document genetic testing, if available
- Further extended study procedures are CDR, ADCS-ADL-MCI, ADAS-Cog13, NPI
- Further optional study procedures are imaging, Qol-AD, Zarit Burden Interview, MPDQ20, RUD-Lite and SF-36

9.2. Follow-up

Following the baseline visit (visit 0), annual follow-up visits are planned as scheduled in clinical routine.

9.2.1. Follow-up documentation – annual visits

During the follow-up visits, the Investigator will:

- Perform and document MMSE, GDS and neuropsychological testing (CERAD-Plus)
- Record blood pressure
- Document height and weight
- Record changes in medication, in particular AD-specific medication
- Document further imaging, if available
- Collect material to the cBMB
- Further extended study procedures are CDR, ADCS-ADL-MCI, ADAS-Cog13, NPI
- Further optional study procedures are imaging, Qol-AD, Zarit Burden Interview, MPDQ20, RUD-Lite and SF-36

9.2.2. Additional documentation during follow-up visits

- If special treatment is available and additional MRI or other study procedures need to be performed, document additional ratings and / or scales

9.3. Withdrawal of Patients from the Registry

Patients must be withdrawn from the registry for any one of the following reasons:

- The patient withdraws consent.
- The physician withdraws the patient from the registry for medical reasons.

The reason for the patient's withdrawal from the study must be dated and recorded in the patient's case report form (CRF).

10. DATA COLLECTION

10.1. Biobank

The RWTH centralized Biomaterial Bank (cBMB) is used as biobank. The documents of this biobank were written according to the Working Group of Medical Ethics - Committees in Germany. Samples taken at sites outside Aachen are collected at the centers and sent to the cBMB in Aachen at short regular intervals. The Advisory Committee (14.2) of the registry decides on the access to the biospecimens. The Advisory Committee has a quorum with a simple majority. The collection of biosamples shall be recorded in the German dementia registry electronic database.

10.2. Assessments

Refer to Section 4 for the timing of assessments. Data (patient characteristics, anamnestic parameter, medication, neurophysiological tests) will be collected during the visits. Additional diagnostic parameters (biomarker, imaging, laboratory parameter) will be documented. Data will be collected by a web-based eCRF. The electronic database will be monitored centrally. Please see for details Supplement.

10.2.1. Demographic data

The following demographic data will be recorded:

- Month and Year of birth
- Sex (male, female)
- Ethnicity
- ISCED education level
- Family history of dementia in the first-degree relatives (negative, positive, not informative)
- Marital status of the patient (unmarried, married/partnership, widowed, divorced)

10.2.2. Diagnosis

- Syndromic classification (SCI, MCI, early dementia)
- Etiological classification (Alzheimer's Disease, Frontotemporal Dementia (behavioral, PPA), Parkinson's Disease, Lewy- Body Dementia, Progressive Supranuclear Palsy, Corticobasal Degeneration, Normal Pressure Hydrocephalus, Vascular Dementia, Prion-Associated Dementia, TDP-43 associated limbic encephalopathy[LATE])

  The diagnosis of Alzheimer's disease, Frontotemporal dementia, Dementia by Parkinson's disease, Lewy-Body dementia, Progressive Supranuclear Palsy, Corticobasal degeneration and Vascular dementia are made according to the S-3 Guidelines for Dementia of Deutsche Gesellschaft für Neurologie [Deutsche Gesellschaft für Neurologie 2016].

  The diagnosis of Normal Pressure Hydrocephalus is made according to the Guidelines for Normaldruckhydrocephalus of Deutsche Gesellschaft für Neurologie (DGN) and

Deutsche Gesellschaft für Neurochirurgie [Deutsche Gesellschaft für Neurologie, Deutsche Gesellschaft für Neurochirurgie 2017].

- Age in years at the time of onset

10.2.3. Physical parameter

- Systolic arterial blood pressure
- Diastolic arterial blood pressure
- Height in meters
- Weight in kg
- Body Mass Index in kg/m^2 (will be automatically calculated)

10.2.4. Medical history / Risk factors

- Smoking status (no, yes, ex-smoker, unknown)
- Smoking in pack–years (counted: packs of cigarettes smoked per day x years of smoking)
- Physical activity in minutes per week (no activity, < 30 min per week, 30 – 60 min, 60 – 90 min, > 90 min)
- Other relevant medical diagnosis (to be selected from ICD-10 diagnosis list and also option to document in text)
- Further information to be included is listed in the attachment Table 2

10.2.5. Treatment

- AD-specific medication (none, memantine, rivastigmine, donepezil, galantamine)
- All other medications at the baseline, changes shall be recorded in follow-up visits
- Non-pharmacological treatment

10.2.6. Mini Mental State Examination total score

The Mini-Mental State Examination (MMSE) is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. The following four cut-off levels classify the severity of cognitive impairment: no cognitive impairment 24-30; mild cognitive impairment 19-23; moderate cognitive impairment 10-18; and severe cognitive impairment ≤9 [Tombaugh and McIntyre 1992].

10.2.7. Montreal Cognitive Assessment total score

The Montreal Cognitive Assessment (MoCA) is a widely used screening assessment for detecting cognitive impairment. It was validated in the setting of mild cognitive impairment, and has subsequently been adopted in numerous other settings clinically. MoCA scores range between 0 and 30. A score of ≥26 is considered to be normal [Nasreddine et al. 2005].

10.2.8. Clinical Dementia Rating Score

The Clinical Dementia Rating (CDR) is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care [Morris 1993]. Scores in each of these are combined to obtain a composite score ranging from 0 through 3:

- 0 – no dementia
- 0,5 – very mild dementia
- 1 – mild dementia
- 2 – moderate dementia
- 3 – severe dementia

10.2.9. ADCS-ADL-MCI

The Alzheimer's Disease Cooperative Study / Activities of Daily Living scale for MCI patients (ADCS/MCI/ADL) is a functional evaluation scale for MCI patients, based on the information provided by an informant/carer, that describes the performance of patients in several activities of daily living. It was adapted by Douglas Galasko and co-workers from the original ADCS/ADL scale, which was constructed to evaluate patients with dementia in the Alzheimer's Disease Cooperative Study, as a measure of the AD patients' performance in ADL [Galasko et al., *Alzheimer Assoc Disord* 1997, 33-39]. For details on item level please see Supplement.

10.2.10. Geriatric Depression Scale total score

The Geriatric Depression Scale (GDS) is a validated 30-item self-report assessment used to identify depression in the elderly [Yesavage et al. 1982]. The user answers 30 question in a yes/no format. One point is assigned to each answer. The following cut-offs are applied:

- 0-9: normal
- 10-19: mildly depressed
- 20-30: severely depressed

10.2.11. Neuropsychiatric Inventory (NPI-10)

The NPI examines 10-sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/aggression, and aberrant motor ability.

10.2.12. Magnetic resonance imaging

- Date of the MRI procedure
- Degree of medial temporal lobe atrophy in the right and left hemisphere, according to Scheltens score (0-4)
- Degree of global cerebral atrophy (0-3)
- Degree of parietal lobe atrophy according to Koedam score (0-3)
- White matter hyperintensities according to Fazekas score (0-3)
- Presence of any strategic infarcts (no, yes)
- Presence of macrohemorrhage (no, yes)
- Number of microbleeds – subcortical
- Number of microbleeds – cortical
- Any other important findings in MRI
- Presence of amyloid-related imaging abnormalities with cerebral edema
- Presence of amyloid-related imaging abnormalities with cerebral haemorrhages

For details on item level please see Supplement.

10.2.13. Functional imaging – Nuclear medicine

- Date of the procedure
- Findings of FDG PET (negative, positive, not done)

  [^{18}F]FDG PET of the brain measures regional glucose use. It is used to differentiate Alzheimer's disease from other dementing processes.
- Findings of DAT scan (negative, positive, not done)

  A DAT scan offers the means to distinguish Parkinson-related syndromes from other neurological diseases.
- Findings of Amyloid-PET (negative, positive, not done)

  The deposition of β-amyloid is considered as one hallmark in the pathogenesis of AD. Amyloid-PET can assist in the diagnosis of AD by detecting the presence or absence of β-amyloid plaques.

10.2.14. cBMB Material

- Date of the procedure
- Type of material collected (Blood, CSF, both)
- Location of storage

10.2.15. CSF (neurodegeneration markers)

- Date of CSF collection
- Exact value (in pg/ml) of Amyloid Beta 1-42 in CSF
- Exact value (in pg/ml) of Amyloid Beta 1-40 in CSF
- Exact value of the ratio: (Amyloid Beta 1-42/ Amyloid Beta 1-40) x10 in CSF
- Exact value (in pg/ml) of Amyloid / Tau ratio in CSF
- Exact value (in pg/ml) of Total Tau in CSF
- Exact value (in pg/ml) of Phosphorylated Tau in CSF
- If available, exact value of NFL in CSF
- Any other important findings or comments on CSF results

10.2.16. Plasma (if available)

- Date of Plasma collection
- Exact value of Amyloid Beta 1-42 in Plasma
- Exact value of Amyloid Beta 1-40 in Plasma
- Exact value of the ratio: (Amyloid Beta 1-42/ Amyloid Beta 1-40) x10 in in Plasma
- Exact value of Amyloid / Tau ratio in in Plasma
- Exact value of Total Tau in in Plasma
- Exact value of Phosphorylated Tau in in Plasma

10.2.17. Other tests

- Status of genetic testing such as APOE, APP, PSEN, MAPT, GRN, C9ORF2 (not made, no pathological findings, if any pathological findings)
- Comments on any other relevant diagnostic procedures

For details on item level please see Supplement.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size Justification

The goal of the research initiative is to enroll as many patients as possible with a particular indication and follow them for an extended period of time. Therefore, no sample size considerations are required.

11.2. Analysis Population

Full analysis set: All patients which have been enrolled in the study and meet the inclusion criteria.

11.3. Methods of Analysis

The primary objective of this registry is to evaluate the current diagnostic and treatment behavior and to follow up on a cohort of patients showing the natural course of disease in patients with cognitive impairment and early dementia . Statistical analysis will be initially mainly descriptive. With larger data sets appropriate statistical analysis will be applied, for example progression rates will be assessed using linear-mixed-effect models, responsiveness outcomes calculated. Data quality audits (identifying missing values, incorrect or out-of-range values, or responses that are logically inconsistent with other responses in the database, specially trained registry personnel can review the data queries to identify possible error trends and to determine whether additional site training is required) will be defined in the data management plan. Data quality will be assessed by describing data completeness (percentages of missing values) every 12 month.

Patient characteristics will be displayed in terms of demographic data and disease characteristics.

Continuous data will be summarized by arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables can also be presented in categories. Categorical data will be summarized by the total number of patients in each category and the number of missing values. Relative frequencies are displayed as valid % (number of patients divided by the number of patients with non-missing values).

11.4. Primary Endpoint Analysis

Not applicable.

11.5. Additional Endpoints Analysis (if applicable)

Analyses referring to special research questions can be conducted if requested and will be described in a separate Statistical Analysis Plan (SAP). Special analyses will be subject to approval by the German Dementia Registry Advisory Committee.

11.6. Interim Analyses (if applicable)

Regular interim analysis is planned every 12 month. This includes the sample size, missing data and drop-outs.

12. ETHICAL REQUIREMENTS

The Sponsor-Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) guidelines and conduct the study according to local regulations. The patient's privacy; physical, mental, and social integrity; and the confidentiality of his or her personal information will be strictly respected in accordance with the World Medical Association Declaration of Helsinki and the Declaration of Taipeh.

12.1. Ethics Committee

The Sponsor-Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Protocol amendments will be subject to the same requirements as the original protocol.

12.2. Patient Information and Consent

Prior to any data collection under this protocol, written informed consent with the approved ICF must be obtained from the patient or patient's legal guardian, as applicable, in accordance with local practice and regulations.

Information about the study and that study participation is voluntary must be explained to the patient or legal guardian. The patient or legal guardian must be given sufficient time to consider whether to participate in the study. A copy of the ICF, signed and dated by the patient or legal guardian, must be given to the patient or legal guardian. Confirmation of a patient's or legal guardian's informed consent must also be documented in the patient's medical record prior to any data collection under this protocol.

Each ICF should contain an authorization allowing the Sponsor-Investigator to use and disclose PHI (i.e., patient-identifiable health information) in compliance with local law.

If the participant agrees to the storage of his/her samples in a biobank, a separate ICF for the cBMB must have been concluded for this purpose.

The signed ICF will be retained with the study records.

12.3. Patient Data Protection

Prior to any data collection under this protocol, candidates must provide all authorizations required by local law.

The patient will not be identified by name in the CRF or in any register reports, and these reports. A list of 100 pseudonyms is created for each center by the Institute for Medical Informatics of the University Hospital Aachen. The pattern looks like xxx-yyy (x= numbers; y= numbers and or letters). Where the first three numbers (x) will have a reference to the center. The values for the y will be generated completely randomly.Ethics committees and various government health agencies may inspect the records of this register. Every effort will be made to keep the patient's personal medical data confidential.

12.4. Compensation for Injury

It is recommended that each center takes out a travel - accident insurance for the participants.

12.5. Conflict of Interest

Investigators should address any potential conflicts of interest with the patient before the patient makes a decision to participate in the study.

12.6. Registration of Study and Disclosure of Study Results

The Sponsor-Investigator will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

13. ADMINISTRATIVE PROCEDURES

13.1. Study Site Initiation

The Investigator must not enroll any subjects into the study prior to all prerequisite study document completion and agreement by the Sponsor-Investigator.

13.2. Study Funding

The work of the Sponsor-Investigator will be financially supported and is open to funding by pharmaceutical companies and industry as it pertains to the conduct of this study. All financial details are provided in separate contracts between the Sponsor-Investigator and the companies. Additional funding from other sources is possible to secure registry set-up and long-term sustainability of the registry.

13.3. Study Completion

The ethics committee must be notified of completion or termination of the protocol. Within 3 months of protocol completion or termination, the Sponsor-Investigator must provide a final clinical summary report to the ethics committee. The Sponsor-Investigator will maintain an accurate and complete record of all submissions made to the ethics committee, including a list of all reports and documents submitted.

13.4. Publications

The Sponsor-Principal Investigator is the owner of the data and has the right to publish or otherwise publicly disclose information describing and/or more generally relating to the registry, and information and data arising from the registry. The Sponsor-Principal Investigator agrees that any publication or other public disclosure shall include an acknowledgment of financial support by pharmaceutical companies and industry and, if applicable, support of the development of the publication or disclosure.

14. FURTHER REQUIREMENTS AND GENERAL INFORMATION

14.1. External Contract Organizations

14.1.1. Electronic or Remote Data Capture

Patient information will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture (EDC) tool.

14.2. Advisory Committee

An Advisory Committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The Advisory Committee will meet at appropriate intervals to monitor patient accrual and to monitor compliance with the protocol at individual study sites. The Advisory Committee will determine whether the study should be stopped or amended.

In addition, the Advisory Committee decides on requests for the use of data. It should be noted that data may be exported pseudonymously if it is a scientific request. If commercial requests are involved, the data will only be released in anonymized form. The committee has a quorum with a simple majority when half of the members are present.

The Advisory Committee, headed by Prof. Schulz, is formed by a vote of the participating sites and includes 6 members. Members to be voted on will be proposed by the heads of the centers.

In case the voting is tied, the vote of the head of the Advisory Committee counts twice.

14.3. Level of data exports

For data requests to the advisory committee only anonymized patient level data will be exported.

14.4. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities as required by local law. Protocol modifications that affect patient safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

In the event of a protocol modification, the patient ICF may require similar modifications (see Sections 12.1 and 12.2).

14.5. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

14.6. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local laws or regulations.

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16. INVESTIGATORS SIGNED AGREEMENT OF STUDY PROTOCOL

I have read the foregoing protocol, "German dementia registry," and agree to conduct the study according to the protocol and the applicable ICH guidelines and local regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

22.12.21

Sponsor-Investigator's Signature Date

Prof. Jörg B. Schulz

Sponsor-Investigator's Name (Print)

Aachen

Study Site (Print)

17. ATTACHMENT

E01 Jodmangelbedingte Schilddrüsenkrkh.u.verwandt.Zustände		I10 Essentielle (primäre) Hypertonie
E03 Sonstige Hypothyreose		I25 Chronische ischämische Herzkrankheit
E11 Nicht primär insulinabhäng. Diabet. mell.[Typ-2-Diab.]		I48 Vorhofflattern und Vorhofflimmern
E66 Adipositas		I49 Sonstige kardiale Arrhythmien
E78 Störungen d. Lipoproteinstoffwechs. u.sonst.Lipidämien		I50 Herzinsuffizienz
F06 And.psych.Stör.wg.Schäd./FktStör.Hirn od.körperl.Krkh.		I63 Hirninfarkt
F10 Psychische und Verhaltensstörungen durch Alkohol		I65 Verschluss und Stenose präzerebraler Arterien ohne resultierenden Hirninfakt
F25 Schizoaffektive Störungen		I67 Sonstige zerebrovaskuläre Krankheiten
F31 Bipolare affektive Störung		I69 Folgen einer zerebrovaskulären Krankheit
F32 Depressive Episode		I70 Atherosklerose
F33 Rezidivierende depressive Störung		I73 Sonstige periphere Gefäßkrankheiten
F34 Anhaltende affektive Störungen		J44 Sonstige chronische obstruktive Lungenkrankheit (COPD)
F40 Phobische Störungen		J45 Asthma bronchiale
F41 Andere Angststörungen		K21 Gastroösophageale Refluxkrankheit
F43 Reaktionen auf schwere Belastungen u. Anpassungsstör.		K29 Gastritis und Duodenitis

F45 Somatoforme Störungen		M15 Polyarthrose
F51 Nichtorganische Schlafstörungen		M50 Zervikale Bandscheibenschäden
G20 Primäres Parkinson-Syndrom		M51 Sonstige Bandscheibenschäden
G25 Sonst. extrapyramid. Krankheiten u. Bewegungsstörungen		M53 Sonst. Krankh. v. Wirbelsäule/Rücken, and.nicht klass.
G35 Multiple Sklerose [Encephalomyelitis disseminata]		M54 Rückenschmerzen
G40 Epilepsie		M79 Sonst. Krkh. d.Weichteilgewebes, anderenorts ni.klass.
G43 Migräne		N40 Prostatahyperplasie
G44 Sonstige Kopfschmerzsyndrome		R26 Störungen des Ganges und der Mobilität
G45 Zerebrale transitor. Ischämie und verwandte Syndrome		R42 Schwindel und Taumel
G47 Schlafstörungen		R55 Synkope und Kollaps
G62 Sonstige Polyneuropathien		H81 Störungen der Vestibularfunktion [38]
G81 Hemiparese und Hemiplegie		H93 Sonstige Ohrkrankheiten, anderenorts nicht klassifiz.
G93 Sonstige Krankheiten des Gehirns		

Table 2 Risk factors