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1. LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
BMI	body mass index
BOÄ	Berufsordnung für Ärzte
cBMB	centralized Biomaterial Bank
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CRF	case report form
CSF	cerebrospinal fluid
DAT	dopamine transporter
eCRF	Electronic case report form
EDC	electronic data capture
EEG	Electroencephalography
FDG	fluorodeoxyglucose
GCP	Good clinical practice
GDS	Geriatric Depression Scale
ICF	informed consent form
ICH	International Conference on Harmonisation
IWG	International Working Group
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)
NFL	neurofilament light chains
PET	positron emission tomography
PHI	protected health information
RDC	remote data capture
SAP	statistical analysis plan
SCD	subjective cognitive decline
TIA	transient ischemic attack

2. SYNOPSIS

Item	Description
Project Title:	German Dementia Registry
CTC-A No.	19-050
Version Number:	6.0
Regulations	The participating sites must ensure that the therapy is carried out in accordance with guidelines or international therapy standards. Therapy planning is done individually according to the patient's situation; no binding therapy guidelines are given. The logged-in user enters the patient's date of consent in the database and confirms that the patient has been properly informed. This process is automatically logged in the database. Patients are registered and tracked in the registry after a positive vote by the ethics committee responsible for the respective sites. The vote is applied for by submitting the project plan as a prospective study in accordance with professional law (§ 15 MBOÄ). Notification to the authorities is not required.
Registry Indication:	SCD, MCI or early dementia of different etiology with biomarkers.
Rationale:	Currently, there is no existing biomarker-based registry for cognitive impairment and 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 long-term data on patients with cognitive impairment and dementia and the impact of treatments.
Design:	Open-ended Registry

Location and Number of Sites:	All sites treating patients with cognitive impairment and 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 sites 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 SCD, 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, TDP-43 associated limbic encephalopathy (LATE), Mixed Dementia AD + VaD, Prion-Associated Dementia) and existing 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 phosphorylated tau, amyloid or tau imaging . Detailed criteria are described in the project plan.

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 SCD, 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; TDP-43 associated limbic encephalopathy (LATE), Mixed Dementia AD + VaD, Prion-Associated Dementia) <u>together with</u> 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 phosphorylated tau, amyloid or tau imaging . 3. At least 18 years of age. **Inclusion Criteria for family member** 4. At least 18 years of age. 5. Patient was included in the registry 6. Family member is strongly involved to the patient's life according to the patient's statement 7. 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. Unwilling to provide informed consent. 2. 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 phosphorylated tau, amyloid or tau imaging. **Exclusion Criteria for family member** 8. Unable or unwilling to provide informed consent.

3. 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 including treatment (e.g. infusion therapy). Additional diagnostic parameters (biomarker, genetics, imaging, laboratory parameter) and adverse events due to treatment will be documented as conducted in clinical routine. Existing neuropsychological data from clinical routine that are not older than 6 months can be used. Follow up visits shall be performed on an annual basis (± 3 months). Infusion therapy will take place on regular intervals (e.g. every two or four weeks). For the annual interval of follow up visits, the baseline visit is always used as a starting point to prevent time lag.

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 (MRI, PET)	10
	Blood & CSF biomarkers, APOE, Genetics	10
	Functional assessments	
	Clinical Dementia Rating Scale (CDR) estimated	**5**
	Alzheimer's Disease Cooperative Study / Activities of Daily Living scale for MCI patients (ADCS-ADL-MCI)	10
	Cognitive assessments	
	CERAD-Plus	**20**
	Neuropsychiatric symptoms assessments	
	Geriatric Depression Scale – 15 Items (GDS-15)	**10**
	Neuropsychiatric Inventory (NPI-12)	10
	PROMs	
	Quality of Life in Alzheimer's Disease (QoL-AD)	5-10
	Zarit Burden Interview (ZBI)	5-10
	Modified Perceived Deficits Questionnaire (MPDQ20)	5-10
	Resource Utilization in Dementia - Lite Version (RUD-Lite)	5-10
	Short Form (36) Health Survey (SF-36)	5-10
	European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L)	5

Core Visit **ca. 90 min**	**Extended Visit** **ca. 105 min**	Optional Visit ca. 120 min

4. INTRODUCTION

4.1. Background

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].

4.2. 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. 2018, Jack 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 SCD, 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.

5. STUDY OBJECTIVES AND OUTCOMES

5.1. Objectives and Outcomes

The primary objective is the development of a registry to collect longitudinal data on patients with cognitive impairment and dementia with fluid 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 phosphorylated tau, amyloid or tau imaging in Germany.

This will allow to evaluate the current diagnostic and treatment behavior and assess the natural history of a cohort of patients with SCD, MCI or 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.

6. STUDY DESIGN

6.1. Study Overview

This is an open-ended prospective longitudinal multicenter registry in adult patients with SCD, MCI or early dementia of different etiology with fluid 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 phosphorylated tau, amyloid or tau imaging. All sites that care for patients with cognitive impairments and 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' family members are asked to answer questionnaires about their family members' 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 dementia, diagnosed in clinical routine who consent to this process in Germany.

6.2. 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 (± 3 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. At each visit participants can decide which data collection they agree to. The end of study is defined as final collection of data.

6.3. Early Termination of Study

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

7. STUDY POPULATION

7.1. Inclusion Criteria

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

9. 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.
10. Participating patients must have a level of cognitive decline of SCD, MCI or early dementia with a clinical diagnosis of 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; TDP-43 associated limbic encephalopathy (LATE), Mixed Dementia AD + VaD, Prion-Associated Dementia together with 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 phosphorylated tau, amyloid or tau imaging .
11. At least 18 years of age.

Inclusion Criteria for family members

12. At least 18 years of age.
13. Patient was included in the registry
14. Family member is strongly involved to the patient's life according to the patient's statement
15. Ability of the participant, as appropriate and applicable, to understand the purpose and risks of the register

7.2. Exclusion Criteria

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

1. Unwilling to provide informed consent.
2. 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.

Exclusion Criteria for family members

16. Unable or unwilling to provide informed consent.

8. STUDY PROCEDURES

Once the study site has been activated for study participation, patients may be enrolled if they have met the inclusion criteria in Section 7.1 and have not been excluded based on the exclusion criteria in Section 7.2.

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

8.1. 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 7.1 and 7.2.

8.1.1. Baseline documentation

After enrolment and registration of patients, the Investigator will document as available, also in eCRF:

- Record demographic data
- Document diagnosis, stage and onset of disease
- Perform and document MMSE, MoCA, CDR_{est}, GDS-15 and neuropsychological testing (CERAD-Plus)
- Document fluid (CSF, blood if available; optional) 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, including infusion therapy and adverse events e.g. infusion reactions, MRI abnormalities (e.g. ARIAs)
- Document brain MRI, if available (optional)
- Document FDG, amyloid and/or tau PET or DAT-Scan imaging, if available (optional)
- Collect material to the cBMB
- Document genetic testing, if available and APOE at baseline for infusion therapy

- Further extended assessments are ADCS-ADL-MCI (family member), NPI-12 (family member),, EQ-5D-5L(extended visit)
- Further optional assessments are Qol-AD (patient/family member), Zarit Burden Interview (family member), MPDQ20, RUD-Lite (family member, without section B1.4) and SF-36 (optional visit)

Existing neuropsychological data from clinical routine that are not older than 6 months can be used.

8.2. Follow-up (± 3 months)

8.2.1. Follow-up documentation – annual visits

- Perform and document MMSE (every 6 months within anti-amyloid infusion treatment), MoCA GDS-15 and neuropsychological testing (CERAD-Plus)
- Record blood pressure
- Document height and weight
- Record changes in medication, in particular AD-specific medication, including infusion therapy and adverse events e.g. infusion reactions, MRI abnormalities (e.g. ARIAs)
- Record changes in Co-morbidities
- Collect material to the cBMB
- Further extended assessments are CDR (patient/family member), ADCS-ADL-MCI (family member), NPI-12 (family member) EQ-5D-5L(every 6 months within anti-amyloid infusion treatment) (extended visit)
- Further optional assessments are imaging, Qol-AD (patient/family member), Zarit Burden Interview (family member), MPDQ20, RUD-Lite (family member, without section B1.4) and SF-36 (optional visit)

8.2.2. 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

8.3. 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.
- If the patient receives legal guardianship due to the increased severity of the illness and this guardian does not agree to further participation

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

9. DATA COLLECTION

9.1. 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 sites and sent to the cBMB in Aachen at short regular intervals. The Steering Committee (14.2) of the registry decides on the access to the biospecimens. The Steering Committee has a quorum with a simple majority. The collection of biosamples shall be recorded in the German Dementia Registry electronic database.

9.2. Assessments

Refer to Section 3 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 remotely.

9.2.1. Demographic data

The following demographic data will be recorded:

- Year of birth
- Sex (male, female, x)
- 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)

9.2.2. Diagnosis

- Level of cognitive decline: SCD, MCI, early dementia at inclusion (oderate and severe dementia when progressed within participation)

  Clinical diagnosis : Alzheimer’s Disease, Frontotemporal Dementia (behavioral, PPA), Parkinson’s Disease, Lewy- Body Dementia, Progressive Supranuclear Palsy, Corticobasal Degeneration, Normal Pressure Hydrocephalus, Major Depression, Vascular Dementia, TDP-43 associated limbic encephalopathy [LATE], Mixed Dementia AD + VaD, Prion-Associated Dementia)

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

9.2.3. 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 in the eCRF)

9.2.4. 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)
- Recording of risk factors: sleep, air pollution, hearing, vision, LDL cholesterol, physical activity and traumatic brain injury
- Physical activity in minutes per week (no activity, < 30 min per week, 30 – 60 min, 60 – 90 min, > 90 min)
- Information (in minutes per week) on physical activity that strengthens strength or promotes endurance
- Other relevant medical diagnosis (to be selected from ICD-10 diagnosis list and also option to document in text)
- Enquiry regarding the use of digital apps to improve cognitive ability (how many hours and minutes)

Further information to be included is listed in the attachment Table 2

9.2.5. Treatment

- AD-specific medication (none, memantine, rivastigmine, donepezil, galantamine, gingko, off-label drugs), changes shall be recorded in follow-up visits
- Infusion therapy (lecanemab, donanemab, others)
- All other medications at the baseline, changes shall be recorded in follow-up visits
- Non-pharmacological treatment

9.2.6. Mini Mental State Examination total score (MMSE)

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].

9.2.7. Montreal Cognitive Assessment total score (MoCA)

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].

9.2.8. Consortium to Establish a Registry for Alzheimer’s Disease (CERAD-Plus)

The CERAD neuropsychological test battery is an assessment tools for the evaluation and diagnosis of patients with Alzheimer’s disease (AD). It assesses brain performance in those functional areas in which specific cognitive deficits can be observed in Alzheimer's type dementia, namely memory, language, praxis and orientation. This test battery has been expanded to include the additional tests Trail Making Test A + B and Phonemic Fluency (S-words) to CERAD-Plus.

9.2.9. Clinical Dementia Rating Score (CDR)

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

9.2.10. Alzheimer's Disease Cooperative Study / Activities of Daily Living scale for MCI patients (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].

9.2.11. Geriatric Depression Scale total score (GDS-15)

The Geriatric Depression Scale (GDS-15) is a validated 15-item self-report assessment used to identify depression in the elderly [Yesavage et al. 1982]. The user answers 15 question in a yes/no format. One point is assigned to each answer. The following cut-offs are applied:

- 0-5: normal
- 5-10: mildly depressed
- 11-15: severely depressed

9.2.12. Neuropsychiatric Inventory (NPI-12)

The NPI examines 12-sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/aggression, and aberrant motor ability.

9.2.13. Perceived Deficits Questionnaire (PDQ)

The Perceived Deficits Questionnaire (PDQ) was developed as part of this program of research. The PDQ assesses the degree to which individuals with debilitating health or mental health conditions experience problems with memory, attention or concentration [Sullivan et. al, 1990].

9.2.14. Quality of Life in Alzheimer's Disease (QoL-AD)

The Quality of Life in Alzheimer's Disease (QOL-AD) proxy allows the assessment of two relevant health-related QoL domains of people with dementia. The QoL-AD is comprised of 13 items and uses a scale of 1–4 (poor, fair, good, or excellent) to rate a variety of life domains, including the patient's physical health, mood, relationships, activities, and ability to complete tasks [Longsdon et al., 1999].

9.2.15. Resource Utilisation in Dementia lite (RUD lite)

The Resource Utilisation in Dementia (RUD) lite is a short version of the RUD structured interview to assess costs of care including patient accommodation, informal care, community care and hospitalizations [Wimo et al., 1998]. The questionnaire was shorted by section B1.4 for this Registry.

9.2.16. Short Form (36) Health Survey (SF-36)

The SF-36 consists of 36 questions and is a general health questionnaire that provides a profile of two summary health components by assessing the patient's health status on 8 different dimensions [Ware, 2000].

9.2.17. Zarit Burden Interview (ZBI)

The Zarit Burden Interview, a popular caregiver self-report measure used by many aging agencies, originated as a 29-item questionnaire [Zarit, Reever & Bach-Peterson, 1980]. The revised version contains 22 items. Each item on the interview is a statement which the caregiver is asked to endorse using a 5-point scale. Response options range from 0 (Never) to 4 (Nearly Always).

9.2.18. European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L)

The EQ-5D-5L can be used to assess the quality of life of patients regardless of their condition. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions [EuroQol Group in 2009].

9.2.19. Magnetic resonance imaging

- Date of the MRI procedure
- MRI Field strength
- 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)
- Degree of medial temporal lobe atrophy according to Scheltens score (0-4)

- White matter hyperintensities according to age-related white matter change (ARWMC) (Fazekas score (0-3)
- Presence of any strategic infarcts (no, yes)
- Presence of macrohemorrhage (no, yes)
- Number of cerebral microbleeds – deep
- Number of cerebral microbleeds – infratentorial
- Number of cerebral microbleeds - cortical
- Any other important findings in MRI
- Presence of amyloid-related imaging abnormalities with cerebral edema (no, yes)
- Presence of amyloid-related imaging abnormalities with cerebral haemorrhages

9.2.20. ARIA-related structural brain imaging

- Radiographic severity for ARIAs
- Presence of microhaemorrhage and radiographic severity
- Presence of superficial siderosis and radiographic severity
- Presence and location of macrohaemorrhage

9.2.21. Functional imaging – Nuclear medicine

- Date of the procedure(s)
- 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.
- Findings of Tau-PET (negative, positive, not done)

9.2.22. cBMB Material

- Date of the collection
- Type of material collected (Blood (serum and plasma [EDTA]), CSF or both)
- Location of storage

9.2.23. 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) 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 of the ratio (Amyloid / Tau ratio) 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

9.2.24. Blood (if available)

- Date of blood collection
- Exact value of Amyloid Beta 1-42
- Exact value of Amyloid Beta 1-40
- Exact value of the ratio: (Amyloid Beta 1-42/ Amyloid Beta 1-40)
- Exact value of Amyloid / Tau ratio
- Exact value of Total Tau
- Exact value of NFL in plasma or serum
- Exact value of phosphorylated Tau

9.2.25. Other tests

- Status of genetic testing such as APOE, APP, PSEN, MAPT, GRN, C9ORF2 (not done, no pathological findings, if any pathological findings, genetic testing results of Amyloid precursor protein, Presenilin 1 and Presenilin 2, and others)
- Comments on any other relevant diagnostic procedures

9.2.26. Adverse Events (AEs)

- Date of observation
- Who has noticed the symptoms?
- Adverse events (yes or no)
- Presence and clinical manifestation of ARIA-E
- Grading of infusion reactions according to Cummings et al., J Prev Alz Dis 2023
- Severity of symptom rating according to Cummings et al., J Prev Alz Dis 2023 for headache, fall, dizziness, arthralgia, urinary tract infection, diarrhoea, fatigue, anxiety, back pain, seizures (0-3)
- Documentation of other adverse events
- Management of ARIA in terms of dosing
- Clinical management and resource of ARIA
- Discontinuation of infusion therapy (yes or no)
- Outcome of AEs

10. STATISTICAL CONSIDERATIONS

10.1. 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.

10.2. Analysis Population

Full analysis set: All patients which have been enrolled in the study and meet the inclusion criteria and no exclusion criteria.

10.3. 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 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 months.

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).

10.4. Primary Endpoint Analysis

Not applicable.

10.5. 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 Steering Committee.

10.6. Interim Analyses

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

11. ETHICAL REQUIREMENTS

The Investigator must comply with all instructions, regulations, and agreements in this project plan 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 Taipei.

11.1. Ethics Committee

The Investigator must obtain ethics committee approval of the project plan, ICF, and other required study documents prior to starting the study at his/her site

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

Project plan amendments will be subject to the same requirements as the original project plan.

11.2. Patient Information and Consent

Prior to any data collection under this project plan, 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 project plan. The declarations of consent can be obtained from physicians participating in the study as well as research assistants employed for the study with at least a Bachelor's degree.

Each ICF should contain an authorization allowing the 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 the biobank (cBMB), a separate ICF for the cBMB must have been concluded for this purpose.

The signed ICF will be retained with the study records.

11.3. Patient Data Protection

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

The Department for Medical Informatics (IMI) of the University Hospital RWTH Aachen, Univ.-Prof. Dr. med. Rainer Röhrig, Pauwelsstraße 30, 52074 Aachen, is responsible for data processing. The data collection is carried out for the purpose of the above-mentioned research project.

Only medical data necessary to achieve the objective of the register will be documented. The personal data collected are: Gender and year of birth as well as telephone number. It is ensured that patient-related data will not be disclosed to third parties at any time. Evaluations are carried out exclusively with pseudonymised or anonymised data. Results of evaluations are published in anonymised form so that it is no longer possible to assign data to individual patients.

The data are protected against unauthorised access by technical and organisational measures - in accordance with the modelling specifications of the Bundesamt für Sicherheit in der Informationsverarbeitung (BSI). Based on the research guideline for Good Clinical Practice, certain authorised persons have a right to inspect the personal data in each site. The inspection only takes place within the scope of their legally regulated tasks for the purpose of reviewing and assuring the quality of the data. These persons are bound to secrecy. The personal data will be completely anonymised after completion of the quality assurance of the research project.

Information allowing the mapping of clinical data to a person will not be stored in this databank. The pattern looks like xxx-yyy (x= numbers; y= numbers). Where the first three numbers (x) will have a reference to the site. The last three numbers (y) will have a reference to the patient. The link between identification-relevant patient data and clinical data is only possible for a limited group. The relevant data protection regulations according to the Federal Data Protection Act are taken into account at all times.

If a patient terminates participation prematurely, no further data will be collected about him/her and the personal and medical data collected up to that point will be completely anonymised.

The patient has the right to inspect his or her data collected during the study. If he discovers errors in his data, he has the right to have them corrected by the investigator. Furthermore, the patient has the right to information and to be provided with a copy of his or her data. Patients also have the right to complain to a supervisory authority about the handling of their data.

After completion of the registry, proper storage and management of all study documents is ensured for up to ten years in accordance with legal requirements. The register database will be completely anonymised immediately after completion of the register and clarification of open points (queries, database closure). A copy of the anonymised data (database export) is handed over to the Institute for Medical Informatics (IMI) of the University Hospital RWTH Aachen for evaluation.

11.4. Compensation for Injury

A separate patient`s insurance is not completed.

In the case of fault-based incidences the patients are insured by the general liability insurance of the Hospital.

It is recommended that each site provides a travel-accident insurance for the patients.

11.5. 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.

11.6. Registration of Study and Disclosure of Study Results

The project was registered and published on DRKS before it started (DRKS00027547). The Sponsor-Investigator will publish post study results regardless of outcome on this publicly accessible website in accordance with the applicable laws and regulations.

12. ADMINISTRATIVE PROCEDURES

12.1. 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.

12.2. 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.

12.3. Publications

The Sponsor-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-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.

13. FURTHER REQUIREMENTS AND GENERAL INFORMATION

13.1. External Contract Organizations

13.1.1. 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.

13.2. Steering Committee

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

In addition, the Steering 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 Steering 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 sites.

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

13.3. Level of data exports

For data requests to the Steering Committee only anonymized patient level data will be exported.

13.4. Changes to Final Project Plan

All project plan amendments must be submitted to the ethics committee as required by local law Project plan 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.

In the event of a project plan modification, the patient ICF may require similar modifications (see Sections 11.1 and 11.2).

13.5. Ethics Committee Notification of Study Completion or Termination

Where required, ethics committees must be notified of completion or termination of this study, and sent a copy of the final clinical summary report or publication by the investigator in accordance with necessary timelines (one year).

13.6. 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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15. INVESTIGATORS SIGNED AGREEMENT OF PROJECT PLAN

I have thoroughly read and reviewed the project plan. Having understood the requirements and conditions of the project plan, I agree to perform the research project according to the project plan, Declaration of Helsinki, Declaration of Taipei and regulatory authority requirements (§ 15 BOÄ, BDSG).

I also agree to:

- Wait until I have received approval from the appropriate IEC/IRB before enrolling any subject in this project.
- Obtain informed consent for all subjects prior to any project-related action performed.
- Changes to the project plan must be made in the form of an amendment that has the prior written approval of the Project leader Univ.-Prof. Dr. med. Jörg B. Schulz, University Hospital RWTH Aachen and of the appropriate IEC/IRB.
- Permit and support project-related remote-based monitoring including provision of source data.
- Provide direct access to all project-related records, source documents, and subject files for the monitor from the CTC-A.
- The content of the project plan is confidential and proprietary to Department of Neurology, University Hospital RWTH Aachen.

With my signature below, I acknowledge receipt of the project plan.

Investigator

Project leader

Univ.-Prof. Dr. med. Jörg B. Schulz
Department of Neurology
University Hospital RWTH Aachen

16. 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

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Univ.-Prof. Dr. med. Jörg B. Schulz Department of Neurology **University Hospital RWTH Aachen**	