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PERSPECTIVE

Patient-related benefits of amyloid PET imaging in dementia: Rationale and design of the German randomized coverage with evidence development study ENABLE

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Abstract

The utility of amyloid positron emission tomography (PET) for the etiological diagnosis of dementia and its impact on functional status of patients in routine care are currently unclear. Here, we describe the design of ENABLE, a randomized controlled two-armed coverage with evidence development (CED) study in Germany. Approximately 1126 patients with mild to moderate dementia of unclear etiology will be randomly assigned to either an amyloid PET or a no amyloid PET group. Patients will be followed-up for 24 months. The study has been registered at the German Clinical Trials Register (https://drks.de/search/de/trial/DRKS00030839) with the registration code DRKS00030839. The primary endpoint of ENABLE is the ability to perform functional activities of daily living at 18 months. Secondary endpoints include change in diagnosis, diagnostic confidence, and cognitive and clinical outcomes of patients. We expect that the CED study ENABLE will inform about patient relevant effects of amyloid PET in routine care. Furthermore, we anticipate that ENABLE will support physicians' and payers' decisions on provision of health care for patients with dementia.

KEYWORDS
activities of daily living, biomarkers, diagnosis, health-care research, randomized controlled trial

Highlights

- Study design focuses on the usefulness of amyloid positron emission tomography (PET) in routine care.
- Study design addresses the patient-relevant effect of amyloid PET.
- Patient representatives were involved in the creation of the study design.
- The study will help improve routine care for people with dementia.

1 | BACKGROUND

Only 40% of patients with dementia receive a formal diagnosis of dementia in the German primary care system,[1] consistent with international data.[2,3] The majority of these diagnoses are without further specification of etiology. Alzheimer's disease (AD) is the most common cause of dementia worldwide.[4] AD patients show typical pathological protein deposits, especially amyloid beta (Aβ), in the brain.[5] *Post mortem* studies to detect these Aβ deposits have suggested that 10% to 30% of diagnoses based on clinical examination are incorrect across different countries.[6] Even in specialized settings, diagnostic uncertainty exists in up to 40% of cases with a dementia syndrome.[7,8] In vivo markers of cerebral amyloid burden include Aβ42 concentration in cerebrospinal fluid (CSF) and cerebral binding of amyloid-sensitive tracers in positron emission tomography (PET).[9] Compared to an amyloid PET reference, up to 40% of a clinically defined clinical trial treatment population was found to be amyloid negative.[10] The discrepancy between amyloid status and clinical diagnosis was even higher in early-stage disease, with up to 50% of clinically defined early-stage AD patients being amyloid negative.[10,11]

Previous work demonstrated that amyloid PET testing can usefully support an unclear diagnosis of dementia or an uncertain diagnosis of AD, increase diagnostic confidence,[12–14] and improve patient management.[15–17] Some preliminary evidence suggests that amyloid PET may also be useful in people with inconclusive CSF biomarker results.[18] In the United States, after amyloid PET, the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study showed a shift in diagnosis from AD to non-AD dementia in 25.1% (95% confidence interval [CI], 24.3%—25.9%) of cases and a shift from non-AD to AD dementia in 10.5% (95% CI, 10.0%—11.1%) of cases.[19] IDEAS also showed a change in patient management in 63.5% of patients with dementia as a result of amyloid PET examination.[19] In a single-center study in the Netherlands, dementia patients with an amyloid PET scan showed lower mortality, reduced institutionalization, and reduced care costs compared to a propensity score–matched sample without amyloid PET.[20] Thus, international data suggest a high diagnostic potential of amyloid PET and an impact on morbidity-related factors of patient care even in the absence of amyloid-specific disease-modifying treatments.

However, there is currently an evidence gap regarding the patient-related benefit of amyloid PET in patients who have an unclear or uncertain diagnosis even after guideline-compliant diagnosis by a specialist. The coverage with evidence development (CED) study ENABLE is designed to fill this evidence gap. The ENABLE study will test the hypothesis that amyloid PET will have a benefit on the functional status of patients.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using "pubmed" and study registries (e.g., clinicaltrials.gov) for coverage with evidence development (CED) studies in Alzheimer's disease. Few previous studies are available (IDEAS, AMYPAD-DPMS) that focused on physician related (diagnostic certainty) and health care-related (hospital admissions) primary endpoints, but not on patient-centered primary endpoints.
2. **Interpretation**: Our findings suggest an evidence gap regarding the impact of amyloid PET on patient-centered functional outcomes in routine care. Secondary analyses should address the costs of care and the possible role of blood markers as predictors of amyloid PET results.
3. **Future Directions**: Our study describes the design of a CED study planned to be conducted between 2023 and 2026. The results of this study will inform about patient relevant effects of amyloid-PET in routine care. It will support physicians' and payers' decisions on provision of health care for patients with dementia.

2 | RATIONALE

ENABLE will compare the influence of guideline-compliant diagnostic and therapeutic management including amyloid PET to guideline-compliant diagnostic and therapeutic management without amyloid PET on patient-relevant outcomes of dementia-related morbidity. The hypothesis is that a specific etiologic diagnosis will lead to more appropriate patient management with positive effects on patients' functional status measured as the absolute value of the Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q)[21] at 18-month follow-up. The target population are individuals with a diagnosis of mild-to-moderate dementia in whom the cause of dementia remains unclear after completion of a guideline-compliant diagnosis or in whom AD is diagnosed, but diagnosis remains uncertain (< 85% certainty by the treating specialist).[15,16]

Amyloid PET examination can contribute to increased diagnostic confidence.[12–14] It may improve the management of people with a dementia syndrome[16,19] for whom an etiological diagnosis is relevant in terms of treatment, but cannot be established with sufficient confidence based on standard diagnostic procedures.

For individual patients with a positive amyloid PET examination and an established diagnosis of AD dementia further investigations may not be necessary and adequate medical care and counseling may be initiated promptly. In patients in whom amyloid PET is negative, AD-specific pharmacotherapy can be omitted or discontinued, thus avoiding unnecessary medication with potential side effects. Further diagnostic steps can also be planned to identify other non-AD dementias. Subsequently, patients and caregivers may benefit from targeted medical and psychosocial care; in the end this may lead to improved preservation of the patients' cognitive and functional abilities.

The design of the ENABLE study is based on two previous studies: the already completed US-based IDEAS study,[19] and the ongoing European Amyloid Imaging to Prevent Alzheimer's Disease Diagnostic and

Patient Management Study (AMYPAD-DPMS).[22] IDEAS was designed as a single-arm observational study involving 16,008 individuals with mild cognitive impairment (MCI) or dementia who met appropriate use criteria for amyloid PET.[23] Primary outcomes were twofold: (1) change in diagnoses, diagnostic certainty, and patient management after PET examination and (2) 1-year hospitalization rates and emergency department visits in study participants compared to a matched control group of Medicare beneficiaries who had not undergone amyloid PET. AMYPAD is a three-armed observational study including patients with subjective cognitive decline (SCD), MCI, or dementia. At baseline, it enrolled 840 participants (244 SCD, 341 MCI, and 255 dementia).[24] Primary endpoint is physician's change in diagnostic confidence after amyloid PET.

Because the design of ENABLE was developed collaboratively with key stakeholders (see section 3.6), the primary endpoint of ENABLE is related to the patients' functional status, namely activities of daily living. This is unlike IDEAS and AMYPAD, which primarily capture a physician-centered endpoint such as physician diagnostic confidence. The underlying assumption for the patient-centered endpoint in ENABLE is that effects of amyloid PET on diagnostic confidence and patient management shown in previous studies translate into patient-relevant outcomes, specifically in patients' everyday capabilities. ENABLE was not designed to replace CSF examination by amyloid PET, but is based on the notion that whenever lumbar puncture can be performed it should be used for evaluation of amyloid status, in agreement with the national dementia guidelines.[25] However, even in memory clinics the average rate of lumbar punctures is low,[26] and in specialist practices in Germany, according to statutory health insurance data from 2016 and 2017, the rate of lumbar punctures for etiological diagnosis of cognitive impairment (MCI or dementia) was below 1%.[27] Different from IDEAS, ENABLE is planned as a randomized two-armed study, comparing a group of patients undergoing amyloid PET to a group of patients not undergoing amyloid PET. In addition, ENABLE is planned to mirror as closely as possible routine care. The target group are only people with mild to moderate dementia at inclusion, excluding people with SCD or MCI. This is related to the fact that biomarker assessments are not yet recommended as a standard in these two diagnostic groups in the national guideline.[27,28]

3 | METHODS

3.1 | Participants

ENABLE will randomize 1126 patients age ≥50 years with a clinical diagnosis of dementia of unclear etiology or of AD with low diagnostic certainty (operationalized as diagnostic certainty <85% according to Grundman et al.[15] and Pontecorvo et al.[16]) after specialist diagnostic workup has been completed according to national guidelines,[25] and in whom CSF diagnostics cannot be performed, are refused, or did not lead to a conclusive result. Patients with a severe stage of dementia or absence of an informant will not be allowed to participate in the study. Detailed inclusion and exclusion criteria are listed in Table 1.

The study is registered at the German Clinical Trials Register (https://drks.de/search/de/trial/DRKS00030839) under DRKS00030839.

3.2 | Setting

Patients will be recruited from about 20 memory clinics in Germany. All participating memory clinics are affiliated with a university hospital, and approximately half of them are additionally affiliated with the Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE). We expect each center to contribute between 20 and 120 participants. Recruiting sites represent dementia care at the university hospital level. These sites will perform guideline-compliant diagnostic work-up at high standard so that the advantage of amyloid PET can be assessed at the highest diagnostic level. Additionally, the participating clinical DZNE sites have standard operating procedures in place for conducting and documenting dementia-related diagnostic procedures.[29] These standard operating procedures will be rolled out to the non-DZNE sites.

To mirror routine care after completing the diagnostic process, patients will be referred back to the referring primary care or specialized (neurologist, psychiatrist, geriatrician) physicians for further medical management (see Figure 1). Similar to routine care, the memory clinic will provide a report with specific recommendations for the referring physician. Adherence to these recommendations will be monitored during study visits, but treating physicians and patients will be free in their management choices.

3.3 | Study design

ENABLE is a two-armed randomized controlled study. The assessments at the memory clinics include clinical history and history by a study partner, neuropsychological testing, a physical and neurological examination, a basic blood test, and structural brain imaging with magnetic resonance imaging (MRI) or computed tomography (CT), and possibly a lumbar puncture. If, after completion of these diagnostic measures, the patient has a diagnosis of mild-to-moderate dementia without sufficient diagnostic certainty of its cause, the patient is eligible for inclusion in the ENABLE study. Participants meeting the inclusion criteria will be informed about study participation, and after written informed consent with the involvement of a family member or (if necessary) legal guardian, the study participant will then be randomly assigned (1:1) to one of the two study arms:

1. Arm 1: An amyloid PET scan is conducted within 4 to 8 weeks after randomization. The amyloid PET scans will be uploaded to a central imaging database and centrally read by independent nuclear medicine specialists. The results will be provided in written form to the physician from the memory clinic, who will decide about possible additional diagnostic tests, disclose diagnosis, and set up the management plan together with the patient and his/her caregiver.

TABLE 1 Key inclusion and exclusion criteria

Inclusion criteria
• Patients of age ≥50 years and of any sex or ethnicity with mild to moderate dementia with unclear cause of dementia (ICD-10 code F03) as well as patients with a diagnosis of AD dementia (ICD-10 codes F00.0, 00.1, 00.2, or 00.9) without sufficient diagnostic certainty (<85%)[15,16] according to national guidelines diagnostics.[25] ○ Guideline diagnostic includes at least a specialist physical and neurological examination and clinical history of the patient and a study partner, neuropsychological testing (including CERAD battery[39]), structural imaging, and basic blood testing. • The criteria are operationalized as follows: ○ The patient has a complaint (reported by the patient or by a caregiver) of cognitive problems that are considered by the managing physician to be possibly due to AD. ○ Mild-to-moderate dementia syndrome: CDR[31] >0.5 and <3 and MMSE[30] >10. ○ Unclear dementia diagnosis or uncertain diagnosis of AD: assessment by the diagnosing specialist(s) that there is an unclear dementia diagnosis or that the diagnosis of AD can be made with < 85% diagnostic certainty, but at the same time there is at least 15% certainty that AD is present, so that it cannot be excluded with certainty. • Lumbar puncture for CSF examination is not possible, refused by the patient, or results were inconclusive. • The patient can tolerate a 20-minute amyloid-PET scan. • A study partner is available for the duration of the study. • Consent by a legal representative or proxy is required for patients unable to consent. • Insured in a statutory health insurance.
Exclusion criteria
• Patients with severe dementia, operationalized as CDR score = 3[34] and/or MMSE score[33] < 11. • Patients with MCI who do not yet meet the severity level of dementia. MCI is distinguished from dementia by a CDR score[31] <1 and the absence of cognitive impairment relevant to daily living as assessed by the treating physician. • Patients with another confirmed condition that can fully account for the cognitive impairment (neuroinflammatory, neuroinfective, or neurodegenerative disease; multiple sclerosis; genetic disorders; HIV; brain injuries; neurosurgery after-effects; major depressive episode; schizoaffective disorder; delusional disorder; delirium). • Patients with a life-threatening unstable medical disease or psychiatric condition that could lead to difficulty in complying with the protocol. • Patients who currently receive an investigational pharmaceutical product or have participated in a clinical trial with an investigational pharmaceutical product within 30 days before screening and/or were administered a radiopharmaceutical within 10 radioactive half-lives before study drug administration. • The patient is a woman who is pregnant, planning to become pregnant, or lactating.

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rationg; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography.

2. Arm 2: No amyloid PET scan is performed. The memory clinic physician will decide on the basis of the available diagnostic information without amyloid PET about possible additional diagnostic tests, disclose diagnosis, and set up the management plan together with the patient and his/her caregiver. Of note, if the treating outpatient physician decides to perform a CSF examination or order an amyloid PET scan sometime later during the study, the patient remains in the study and in the originally assigned study arm. The fact that a CSF examination or an amyloid PET scan has been conducted outside the study protocol will be recorded.

An overview of the visit schedule is given in Table 2. The study will include seven mandatory on-site visits (six for control arm without amyloid PET) and one safety telephone visit (3 months after randomization). The on-site visits encompass two or three visits at baseline (screening, baseline, and amyloid PET [only in Arm 1]) and four follow-up visits (months 6, 12, 18, 24).

The screening visit will include patient consent, verification of guideline-compliant diagnostic procedures prior to study inclusion and verification of inclusion/exclusion criteria, as well as collection of the Mini-Mental State Examination (MMSE)[30] and Clincial Dementia Rating (CDR)[31] scores. After consent, study-relevant data on the previous diagnostic procedures will be transferred to the electronic study database (electronic data capture system secuTrial). The baseline visit includes an additional check of the inclusion/exclusion criteria, as well as a medical history, physical/neurological examination, and collection of the primary and secondary endpoint scales and tests. Finally, the baseline includes randomization to the amyloid PET or the no-amyloid-PET arm. Starting from the baseline visit, adverse events (AEs), serious adverse events (SAEs), and adverse drug reactions (ADRs) of any origin will be documented throughout all study visits (see Table 3 for definitions). During a telephone visit at month 3, AEs, SAEs, and ADRs will be queried as well.

During baseline and follow-up visits, clinical examinations will be performed and clinical scales will be applied (see section 3.4), and recorded in pseudonymized form by the study personnel in the electronic study database.

In addition to the CED study examinations, participants will be asked to participate in a blood collection for additional research purposes. As part of this examination, a maximum of 40 mL of blood will be drawn at the baseline and at 12- and 24-month visits. The blood samples will be stored pseudonymously in the biobank of the DZNE and will be

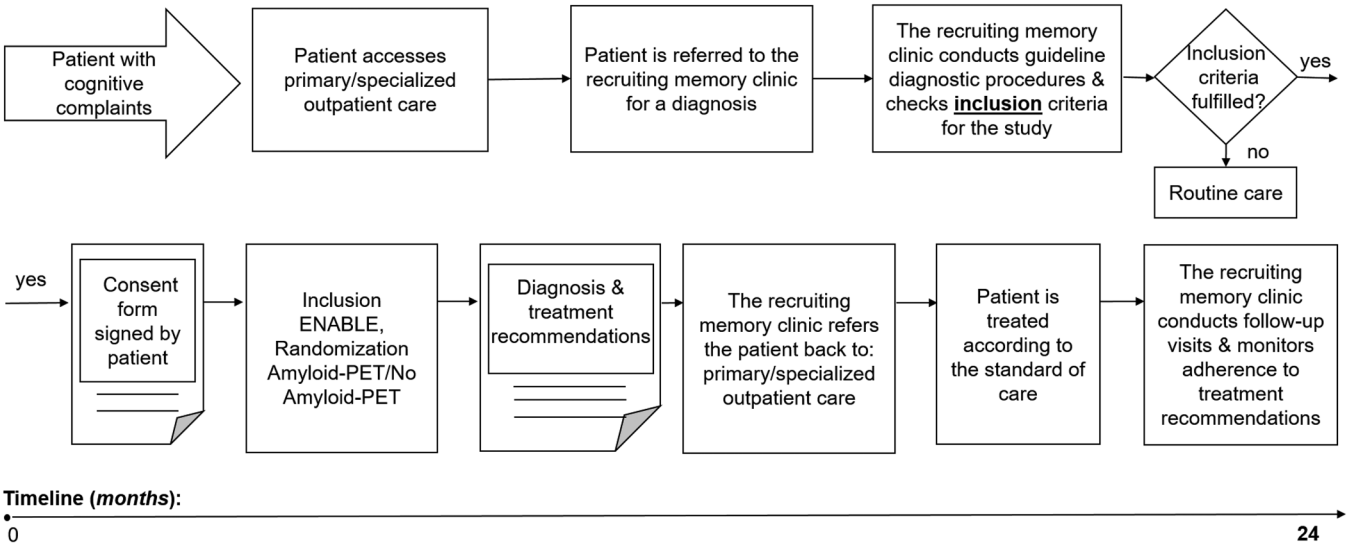

FIGURE 1 Exchange between treating outpatient physicians and the recruiting memory clinics. The flowchart represents, by means of logic models,[47] the processes and exchanges from the first point of contact (i.e., patient with cognitive complaints access the health-care service) to the next steps of diagnosis, study recruitment, treatment recommendations, and follow-up. Legend: arrow = trigger/input that starts the process; square = a partial step into the process; diamond = a decision (yes/no); document = a result/deliverable (e.g., report or formal document). PET, positron emission tomography

available for further scientific analysis. Participation in the scientific blood sampling is not a prerequisite for participation in the CED study.

3.4 | Endpoints

The primary endpoint is the ability to perform activities of daily living. This endpoint will be measured using the A-IADL-Q[21] (primary endpoint: score at 18 months after randomization). The instrument was developed and validated according to the methodological requirements of the US Food and Drug Administration (FDA) for the collection of patient-reported outcomes.[1] A validated German version is available. The scale has already been used in longitudinal observational studies and showed a high sensitivity for changes in disease progression.[32,33] There is a short version of the scale with 30 items, which has very similar psychometric properties.[34] Because of its simpler handling, the short version will be used as the primary endpoint in a paper/pencil version. Both subscores and summary scores will be recorded. The summary score will serve as primary endpoint.

Secondary and exploratory endpoints are listed in Table 4. The primary endpoint and the secondary endpoints will be collected at the clinical trial sites by trained raters who are blinded to the patient's study arm.

3.5 | Amyloid PET and central reading

For amyloid PET, the two commercially available tracers Vizamyl ([^{18}F]Flutemetamol, GE Healthcare) and Neuraceq ([^{18}F]Florbetaben, Life Radiopharma Berlin GmbH) will be used, which are approved in Germany. For the detection of neuritic plaques in the brain, these tracers are equivalent. We aim for each of the two tracers to be used in ≈50% of the study sites and in ≈50% of the patients.

The amyloid PET examination will be performed and assessed as specified by the approved use of the respective tracer. For Vizamyl, an activity dose of 185 MBq ± 10% will be administered intravenously and for Neuraceq a dose of 300 MBq ± 20%.

We have provided only a few specifications for the PET scanners to allow for subsequent generalizability in routine settings. The use of stand-alone PET, PET/CT, and PET/MRI scanners is allowed, provided they have full-ring systems and allow 3D-mode acquisition of the whole brain (including cerebellum) in a single bed position. Compliance with these basic requirements will be assessed by digital imaging and communications in medicine (DICOM) header check and visual inspection of image quality and artifacts in Hoffman 3D brain phantom scans generated as part of site qualification.

The acquired image data will be pseudonymized and transferred to the imaging server of the contract research organization, which monitors the quality of PET data, and provides the PET reporting (Figure 2). To ensure uniform reporting of amyloid PET, the images will be evaluated centrally by a diagnostic committee consisting of two independent nuclear medicine specialists who are trained for both amyloid tracers. These specialists will be independent of the rest of the study and will not be involved in patient management. In case of discordant findings between the two expert readers, a third expert will be consulted. The (final) binary visual assessment, that is, "amyloid negative" or "amyloid positive," will be reported in written form to the physician at the memory clinic site. Only the central PET reads will be shared with the treating physicians during the study.

TABLE 2 Visit schedule.

Examination/procedure	Screening	Baseline	Amyloid-PET[c]	Phone visit	Follow-up			
	Week −12 to 0		Week 4 to 8 after randomization	Week 13 ± 2 weeks	Week 26 ± 2 weeks	Week 52 ± 2 weeks	Week 78 ± 2 weeks	Week 104 ± 2 weeks
Visit		V0	V1	V2	V3	V4	V5	V6
Review of previous examinations for completeness according to S3 guideline and transfer to database	X							
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Vital signs		X			X	X	X	X
Medication		X			X	X	X	X
Medical history		X			X	X	X	X
Physical/neurological examination (clinical phenotype)		X				X		X
A-IADL-Q		X			X	X	X	X
MMSE	X	X			X	X	X	X
CDR-SB	X	X			X	X	X	X
Randomization		X[6]						
ADAS-Cog		X			X	X	X	X
QOL-AD		X			X	X	X	X
FIMA					X	X	X	X
EQ-5D-5L (self and proxy)		X			X	X	X	X
GDS		X			X	X	X	X
(S)AEs and ARs			X	X	X	X	X	X
PRISCUS list[a]		X			X	X	X	X
Adherence to guidelines[b]					X	X	X	X
Amyloid PET[c]			X					
Phone visit				X				
Optional blood sampling		X				X		X

[a]The PRISCUS list was commissioned by the Federal Ministry of Health for the German health-care system; it lists potentially unsuitable drugs with reasons and suggests alternative preparations.[40] It is evaluated by medical review.
[b]Specifically, anti-dementia pharmacotherapy, medication review, initiation of specific counseling, and specific psychosocial interventions.
[c]Amyloid PET examination will be performed only in the group randomized to this arm.
Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; A-IADL-Q, Amsterdam Instrumental Activities of Daily Living Questionnaire; AR, adverse reaction; CDR-SB, Clinical Dementia Rating Sum of Boxes; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; FIMA, questionnaire for health-related resource use in the elderly; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; PET, positron emission tomography; PRISCUS, potentially inappropriate medications in the elderly; QOL-AD, Quality of Life in Alzheimer's Disease; (S)AE, (serious) adverse events.

3.6 | Generation of the study design

As a CED study, the design of the ENABLE study is closely linked to legislation of the German fifth code of social law (Sozialgesetzbuch V, §137e). The creation of the CED study included several formal advisory board meetings with members of the Joint Federal Committee (Gemeinsamer Bundesausschuss [G-BA]) and stakeholders. The stakeholders included representatives from health-care insurance companies, the hospital federation, association of statutory health insurance physicians, patient representatives, representatives from the German Institute for Quality and Efficiency in Health Care (IQWiG), and biostatisticians. Additionally, representatives of the professional societies for neurology, psychiatry, radiology, and nuclear medicine; representatives from the manufacturer companies; and members of the DZNE and external biostatisticians were invited.

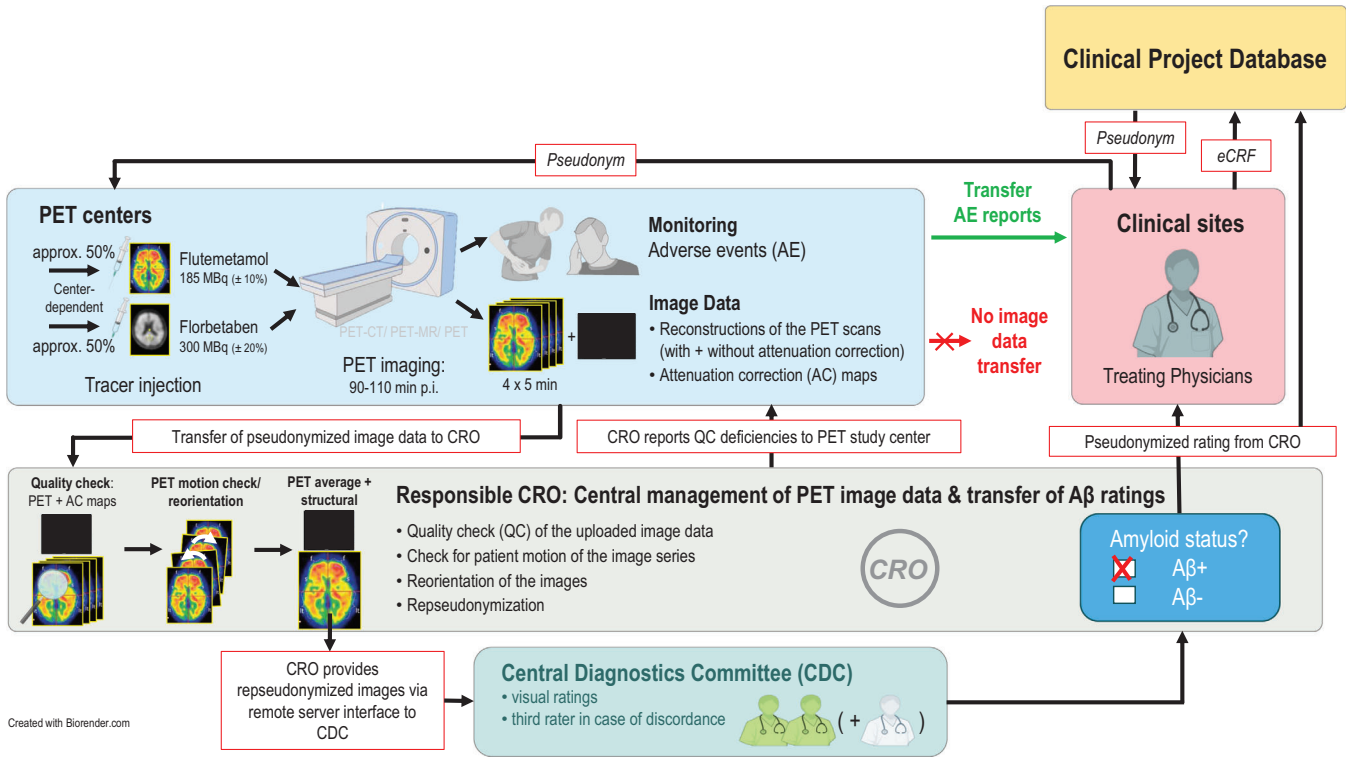

FIGURE 2 Acquisition and reading of amyloid PET scans. Participating nuclear medicine departments perform the PET scans and forward them to the central reading facility at the CRO, which performs quality control and visual assessment of amyloid status. Amyloid status is reported to clinical centers only by the central reading facility, not by local nuclear medicine departments. The local nuclear medicine departments monitor adverse events of PET examinations and report them to the referring clinical sites as appropriate. Aβ, amyloid beta; AE, adverse event; CRO, contract research organization; CT, computed tomography; eCRF, electronic case report form; MRI, magnetic resonance imaging; PET, positron emission tomography

TABLE 3 Definitions for safety monitoring.

A) Safety of amyloid PET
AEs/SAEs/ADRs will be recorded within a time window of 14 days by the respective nuclear medicine department during a telephone call with the patient/caregiver and their connection with amyloid PET will be evaluated using established standards of AE/SAE/ADR reporting.
The frequency of amyloid-related events is expected to be very low, that is <1%.
B) AE/SAE/ADR across the entire study
The goal here is to capture AEs/SAEs/ADRs as a secondary endpoint during each follow-up visit to test whether SAE/AE/ADR frequency is reduced as a consequence of improved diagnostics using amyloid PET, including but not limited to because specific medication can be used more adequately.

Abbreviations: ADR, adverse drug reaction; AE, adverse event; PET, positron emission tomography; SAE, serious adverse event.

3.7 | Statistical planning and analysis

Power analysis suggests that with 394 measurements per group, a one-sided two-group *t* test at significance level 2.5% has 80% power to detect superiority of the amyloid PET arm with respect to mean A-IADL-Q scores at 18 months, with an effect size of Cohen's *d* of 0.2. Assuming a common standard deviation of about 12 points based on previous evidence,[35] $d = 0.2$ corresponds to 2.4 A-IADL-Q score points, the minimal clinically relevant difference according to Dubbelman et al.[36] Anticipating a rate of 30% missing values due to drop-outs after 18 months, $788/0.7 \approx 1126$ patients should be randomized. The primary confirmatory intention-to-treat analysis will evaluate all randomized patients. The effect of allocation to amyloid PET on the A-IADL-Q score 18 months after randomization will be estimated in a linear model including randomized intervention, center, and baseline A-IADL-Q score as independent variables. Multiple imputation will be used to replace missing values. The one-sided 2.5% α-level test to demonstrate superiority of the amyloid PET arm will be based on the corresponding two-sided 95% CI.

To evaluate secondary endpoints, mixed linear models for repeated measures with comparable independent variables as in the primary analysis will be used to evaluate the A-IADL-Q scores from baseline to 24 months after randomization as well as the Alzheimer's Disease Assessment Scale Cognitive subscale, MMSE, CDR-Sum of Boxes, Quality of Life in Alzheimer's Disease, and European Quality of Life 5 Dimensions 5 Level Version. Negative binomial regression will be used to describe the total duration of unplanned hospital admissions.

TABLE 4 Secondary and exploratory endpoints.

Secondary endpoints
• Assessed at the PET center in a period of 14 days after the amyloid PET examination. ■ Occurrence of AE/SAE/ADR related to amyloid PET. • Assessed at the memory clinic study site: ○ 6 months after randomization: ■ Change in etiologic diagnosis of dementia. ■ Change in diagnostic certainty. ■ Change in diagnostic and therapeutic (especially medication administration or discontinuation) management. ○ Throughout the study period: ■ Incidence of AEs and SAEs and ADRs. ■ Mortality (also in the context of the safety assessment). • Assessed by the blinded rater: ○ Functional status (A-IADL-Q,[21] secondary at 6, 12, and 24 months after randomization). ○ Baseline, 6, 12, 18, and 24 months after randomization: ■ Cognitive performance (ADAS-Cog,[41,42] MMSE,[30] CDR score[31]). ■ Quality of life, including health-related quality of life (QoL-AD,[43] EQ-5D-3L[44,45]). ■ Need for full inpatient or institutionalized outpatient care (institutionalization) or intensification of institutionalized outpatient care, and total duration and frequency of unplanned hospital admission within 1 year (FIMA questionnaire[46]). • Assessed by study physician: ○ Use of potentially inappropriate medications: PRISCUS list.[40]
Exploratory endpoints
• Effect of amyloid PET on health economic outcomes. • Association of blood markers of amyloid pathology with qualitative (reading) and quantitative outcomes of amyloid PET. • Association of additional early PET acquisition and quantitative amyloid PET measures with patient cognitive and functional change.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive subscale; AE, adverse event; A-IADL-Q, Amsterdam Instrumental Activities of Daily Living Questionnaire; ADR, adverse drug reaction; CDR, Clinical Dementia Rating; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; FIMA, questionnaire for health-related resource use in the elderly; MMSE, Mini-Mental State Examination; PET, positron emission tomography; PRISCUS, potentially inappropriate medications in the elderly; QOL-AD, Quality of Life in Alzheimer's Disease; SAE, serious adverse event.

AEs will be coded using the Medical Dictionary for Regulatory Activities. The difference in the corresponding rates of SAEs, ADRs, and use of potentially inappropriate medications per treatment arm will be reported with two-sided 95% CIs based on Wilson scores (without continuity correction, method 10 in Newcombe[37]). Mortality rates will be estimated using the Kaplan–Meier method.

4 | EXPECTED OUTCOMES

ENABLE is powered to detect primarily patient-related endpoints, such as functional abilities. The selection of endpoints reflects how the ENABLE study design was developed through four rounds of intensive discussions with stakeholders, including patient representatives. ENABLE will use a randomized controlled design so that effects of amyloid PET can be compared to a control sample recruited in parallel, rather than with a retrospectively collected care cohort. This is relevant, because dementia care in Germany has been improving over the years so that a historical cohort for comparison may be biased in this regard.

ENABLE is closely linked to the German health-care system and its procedures are designed to mirror routine care as well as possible. At the same time, ENABLE introduces modest improvements in dementia health care by providing central training of memory clinics and referring outpatient physicians in dementia diagnosis and treatment. In addition, ENABLE tests a centralized reading of amyloid PET scans. The potential effect of central reading can be tested after completion of the study by comparing outcomes of the central reading to retrospective local reading. The key deliverable of ENABLE will be data for the joint federal body (G-BA) if amyloid PET should be reimbursed by public health insurance in Germany or not.

The CED study falls under strict legislative regulation with a predefined set of endpoints and analyses that mirror routine care as closely as possible. At the same time, in alignment with the G-BA, the study will be extended by three exploratory modules to leverage the resources for further scientific analyses. These analyses will include:

1. Effects of amyloid PET on costs of health care; data on this topic is still scarce in the German health-care system.
2. Associations of blood markers of amyloid and neurodegeneration with amyloid PET data to examine the accuracy of blood markers when used in a multicenter routine care setting.
3. Association of early amyloid PET perfusion frames and of semi-quantitative amyloid PET analysis with patient-relevant outcomes, blood markers, and health-care costs. Semi-quantitative amyloid PET analysis, consideration of partial volume effects, and staging of amyloid deposition in the brain have been shown to be more accurate than binary PET readings for predicting cognitive decline in research cohorts.[38] ENABLE will be providing data to assess this in a health-care cohort.

Recruitment risks have to be considered. Approval of an anti-amyloid treatment by the European Medicines Agency (EMA) within the study period could result in patients' reduced interest in participating in a randomized trial in which they could be randomized to non-amyloid PET. In the spring of 2022, the application of the anti-amyloid antibody aducanumab (ADUHELM) for approval by the EMA has been withdrawn by the company. Another anti-amyloid antibody, lecanemab, was approved in January 2023 by the FDA; a decision by the EMA is expected later in the year 2023. In the event of EMA approval, we estimate that there would be an overlap of 20% of cases between the target population of the ENABLE study and the group of patients for whom anti-amyloid treatment could be considered at all, that is, people with prodromal and mild AD dementia. Therefore, approval of anti-amyloid treatments would have moderate impact on recruitment, which may be compensated by the addition of more study sites. The study comes with a risk of a negative finding given the functional endpoint. A clear negative finding would be informative from the perspective of the health-care system. We will examine whether a minimally important difference can be excluded.

In conclusion, use of biomarkers for the etiological diagnosis of dementia, including amyloid PET, should be evaluated against relevant patient related outcomes. The effects of these outcomes on health-care costs are important for payers. There remain many gaps in improving health care for people with dementia in Europe and internationally. CED studies such as IDEAS, AMYPAD, and ENABLE will help to fill these gaps. At the same time, they will provide blueprints and platforms for the evaluation of other dementia health-care interventions in the future.

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CONFLICT OF INTEREST STATEMENT

The study protocol was developed in several rounds of consultation with the Federal Joint Committee (G-BA) and other stakeholders. These stakeholders included representatives from manufacturing companies, including Life Molecular Imaging GmbH and GE Healthcare. The involvement of manufacturers is an essential part of the creation of a CED study with the G-BA. Stefan Teipel participated on scientific advisory boards of Roche Pharma AG, Grifols, Biogen, and MSD, and is a member of the Independent Data Safety Board of the study ENVISION (Biogen). Erika Graf received consultancy honoraria from Roche Pharma AG. Annika Spottke, Henning Boecker, Marcel Daamen, Jörg Sahlmann, Ralph Buchert, Wolfgang Mohnike, Konrad Mohnike, Jens Kurth, Frank Jessen, and Bernd J. Krause have no disclosures to report. The study ENABLE will be funded by the Federal Joint Committee (G-BA). Author disclosures are available in the supporting information.

CONSENT STATEMENT

This confirms that consent was not necessary, because no research activities were performed with human subjects for preparation of the study design.

ENDNOTES

[1] Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. https://www.fda.gov/media/77832/download

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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