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APPLICATION FOR ETHICAL APPROVAL

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Decision-making, Ethical Consent, and Interactive Dialogue in Ongoing Neurocognitive Decline - DECISION

Version 4.0 (07-07-2025)
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DECISION: Decision-making, Ethical Consent, and Interactive Dialogue in Ongoing Neurocognitive Decline

Project Sketch

As the ability to consent to study participation may be limited in patients with Alzheimer's disease (AD) or related disorders, a precise assessment is essential. However, no standardized procedure exists, despite evidence that consent capacity fluctuates in psychiatric disorders, particularly dementia. The MacArthur Competence Assessment Tool (MacCAT-T) is effective but impractical for routine clinical use due to its complexity. (1) This study aims to develop a simple yet valid instrument for assessing consent capacity in patients with neurodegenerative and vascular dementia, applicable to broader psychiatric settings. Legally, consent capacity requires insight, judgment, and control. These aspects should be operationalized using attention, language comprehension, risk assessment, and situational transfer, structured in a graduated, easily comprehensible format. (2) To validate our findings, we will use the MacCAT-T as a reference alongside the Clinical Dementia Rating (CDR) for overall cognitive function. (3) Additionally, the Cognitive Failures Questionnaire (CFQ) will be examined as a potential screening tool to identify individuals requiring further consent capacity evaluation. (4) Furthermore, we will investigate the correlation between vascular and neurodegenerative lesions and consent capacity. Using a 3 Tesla MRI at the Department of Psychiatry, we will analyze associations between regional nerve cell loss and microbleeds. Biomarkers of neurodegeneration and vascular damage, including platelet-derived growth factor, fibrinogen, pentraxin, and vascular growth factor, will be assessed using the Lumipulse platform (Fujirebio) at the Department of Laboratory Medicine.

As treatments for early AD emerge, there is a growing need for efficient, scalable cognitive assessments. Digital cognitive test batteries offer a promising solution, enabling early detection of mild cognitive impairment, subjective cognitive decline, and dementia. Digitalization can facilitate the widespread implementation of these assessments, making them more accessible and applicable in clinical practice.

Major aims

Primary endpoint: Development of a reusable procedure for assessing the capacity to consent that can also be transferred to other areas of psychiatry
Secondary endpoint: Investigation of whether and to what extent vascular and neurodegenerative lesions correlate with a restriction of the ability to give consent.

This study addresses the challenge that although capacity to consent is a multifaceted construct involving interacting factors such as language, attention, understanding of the problem, and ability to apply these to one's own situation, it is currently assessed using standardized methods and is left to the subjective judgement of individual clinicians. Currently, capacity to consent is assessed using non-standardized methods and is left to the subjective judgement of individual clinicians.

Responsibilities and Funding

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Funding	This study is funded by the Pesl Alzheimer Stiftung.

Scientific Background

Especially in patients with Alzheimer's disease (AD), vascular encephalopathies or mixed forms of dementia, the ability to give consent can be impaired even in the early stages of the disease, which poses a considerable challenge for diagnostic and therapeutic care. (5) (6) (7) (8) Frontal and parietal networks are crucial for self-perception, error judgement and information integration. (9) Their damage, e.g. due to vascular lesions or neurodegenerative diseases such as AD, Lewy body dementia or frontotemporal dementia, can lead to anosognosia. (10) This symptom complicates the assessment of capacity to consent, as it impairs the realistic assessment of one's own illness and its consequences. In addition to the capacity for insight, the judgement and control skills necessary for informed decisions are also affected. The

consideration of anosognosia is therefore of central importance in the development of an assessment instrument.

Study design

This study is designed as a prospective cohort study to develop and validate a structured assessment tool for consent capacity. The study consists of multiple steps, beginning with the identification of potential risk groups through screening, followed by detailed psychometric testing, item selection for test refinement, and validation against established gold-standard measures. By systematically evaluating cognitive and neuropsychological characteristics, we aim to create an accessible, efficient, and valid assessment instrument.

For the DECISION study, a clearly defined, heterogeneous sample of 100–150 individuals will be recruited, including persons with limited capacity to give consent. All participants will be accompanied by a trusted individual who can provide information about their everyday functioning. Participants will be specifically recruited from the ActiGlia and Amy-Clear studies (project numbers 17-755, 17-569, and 18-606), for which comprehensive neuropsychological, clinical, and biomarker-based diagnostics (e.g. cerebrospinal fluid analysis and amyloid/tau PET imaging) have already been performed. Where available, these existing diagnostic results will be re-used with the participants' informed consent, in order to avoid additional invasive procedures such as repeat lumbar punctures. This approach ensures a high degree of diagnostic accuracy while minimizing participant burden. The strictly defined selection process will create a reliable foundation for test development. This careful recruitment strategy will ensure both diagnostic precision within the Alzheimer's continuum and the inclusion of a robust, well-characterized comparison group.

Phase 1: Neuropsychological operationalisation of consent capacity

Phase 1 focuses on the neuropsychological development and validation of this test procedure. To this end, we specifically assess cognitive domains that are related to decision-making ability: attention, executive functions, cognitive flexibility, language comprehension and production, risk assessment, cognitive complaints, as well as aspects of decision-making behaviour and problem-solving ability.

Questionnaires and screening instruments

- Cognitive Failures Questionnaire (CFQ): Assesses subjectively experienced cognitive impairments in everyday life (e.g. forgetfulness, distractibility, impulsive behaviour) and is also suitable for the early detection of atypical forms of dementia (e.g. frontotemporal or vascular dementia). (4)
- Subjective Cognitive Decline Questionnaire (SCD-Q): Assesses subjectively perceived cognitive changes compared to previous performance levels, particularly in relation to memory, attention and language, to identify individuals at risk of developing Alzheimer's disease. (11) (12)
- Dysexecutive Syndrome – External Rating (DEX-F): Assesses changes in executive functioning, such as impulse control, planning, problem solving and emotion regulation, through external assessment by relatives or professional caregivers. (13) (14)

Gold standard for validation

- MacArthur Competence Assessment Tool for Treatment (MacCAT-T): Serves as an established reference standard for assessing capacity to consent. (7)
- Clinical Dementia Rating (CDR): Used for comprehensive assessment of the severity of cognitive impairments. The CDR evaluates six functional areas (e.g. memory, orientation, judgement, social skills) based on external and self-assessments. (8)
- Clock drawing test (CDT): used as a screening tool; errors may indicate impaired consent capacity in Alzheimer's disease (15) (16)

Neuropsychological test battery ('DECISION test battery')

- Aachen Aphasia Test (AAT) for the targeted assessment of language skills: (17)
  - Token test (language comprehension)
  - Spontaneous speech analysis (linguistic expression based on a picture)
  - Written language (reading and writing skills)
- Trail Making Test A/B (TMT): Assesses attention and cognitive flexibility. (18) (19)
- DOSPERT: Assesses risk perception and decision-making behaviour in various everyday contexts. (20)
- PCRS (Patient Competency Rating Scale): Assesses insight into illness from the patient's own perspective and that of others. (21)
- Hooper Visual Organization Test (VOT): Assesses visual object recognition and integration using fragmented images of everyday items (e.g., a disassembled chair). (22)

The modules provide a comprehensive picture of decision-making ability, including subjective, linguistic and behavioural aspects. Language tests are central to this, as language is fundamental to understanding medical information and formulating decisions. Aspects such as insight, values and emotional stress are assessed by other components of the test battery.

Validation Concept (Phase 1)
In Phase 1, several types of validity will be examined to ensure the robustness and practical relevance of the DECISION tool. The following validation strategies will be applied:

Criterion validity will be assessed by comparing the results of the DECISION tool with those of a recognized gold standard—the MacArthur Competence Assessment Tool for Treatment (MacCAT-T). Correlational and regression analyses will be conducted, with a correlation coefficient (r) greater than .5 and a significance level (p) below .05 servingas the benchmarks for sufficient criterion validity.Construct validity will be evaluated by analyzing the relationship between the DECISION tool and

various cognitive measures, including the Trail Making Test A/B (TMT A/B), the Action Affinity Task (AAT), the Domain-Specific Risk-Taking Scale (DOSPERT), the Cognitive Failures Questionnaire (CFQ), and the Patient Competency Rating Scale (PCRS). Correlation and factor analyses will be used. Correlations above .3 and theoretically consistent patterns will be considered indicative of construct validity. To examine convergent validity, the DECISION tool will be compared to other established instruments assessing judgment capacity. Correlational and regression analyses will be carried out, and convergent validity will be assumed if correlations exceed .4 ($r > .4$),

the results are statistically significant ($p < .05$), and the associations are conceptually sound. Discriminant validity will be tested by comparing individuals with Alzheimer's disease (diagnosed based on biomarker evidence) to healthy controls. ROC analysis, AUC values, and t-/U-tests will be used. An AUC above .80 and sensitivity/specificity values above 75% will be considered indicative of strong discriminative power. To confirm structural validity, the internal structure of the DECISION subtests will be examined using factor analysis. Structural validity will be assumed if the model explains more than 50% of the variance and if items clearly load on the expected factors.

Additionally, we aim to identify relevant items from the subtests and examine the possibility of shortening the tests. We also seek to integrate the naming and language comprehension assessment into a single test to streamline the evaluation process.

The short version of an informed consent scale, consisting of subcomponents from the Trail Making Test (TMT A & B), the subtests from the Aachener Aphasia Test (Token-Test and Naming), the Domain-Specific Risk-Taking Scale (DOSPERT), and the Problem Solving Inventory for Adults (PSI-A), which was tested with existing informed consent questionnaires, will be re-presented to the relevant patient group.

For the DECISION study, a clearly defined, heterogeneous sample of 100–150 people will be recruited, including those with limited capacity to give consent. All participants will be accompanied by a trusted individual who can provide information about their everyday functioning. Participants will be specifically recruited from the ActiGlia and AmyClear studies (project numbers 17-755, 17-569 and 18-606), for which comprehensive neuropsychological, clinical and biomarker-based diagnostics (e.g. cerebrospinal fluid analysis and amyloid/tau PET imaging) have already been performed. This will enable precise classification within the Alzheimer's continuum or as healthy controls. The strictly defined selection process creates a reliable basis for test development. This careful selection ensures high diagnostic certainty within the Alzheimer's continuum and a robust comparison group.

Co-design approach

The process development follows a participatory co-design approach that consistently incorporates the perspectives of people with cognitive impairments. The aim is research on an equal footing – with shared responsibility, barrier-free participation and competence promotion. Co-design strengthens motivation, enables early identification of obstacles and allows for iterative adaptation. Findings from interviews with affected

individuals, relatives and carers are incorporated into the comprehensibility, relevance and practicality of the modular test battery.

Guided interviews and medical practice perspectives

In addition, focus groups and guided interviews are conducted with medical professionals who regularly decide on the capacity to give consent. Standardized case vignettes are used to record decision-making processes, uncertainties and routines. The aim is to derive practical requirement profiles that are directly incorporated into the development of the test items and ensure the clinical applicability of the procedure. In the long term, this will result in an evidence-based, practical instrument for assessing consent capacity. 'The focus groups with medical professionals will be recruited separately via a standardised invitation letter. Separate informed consent will be obtained. Audio recordings will be stored pseudonymously, archived with password protection and deleted after completion of the evaluation.'

Legal evaluation and interdisciplinary integration

The procedure will be evaluated from a legal perspective to strengthen its legal applicability. The legal evaluation of the informed consent procedure will be conducted by an external specialist in medical law with specific expertise in research ethics and dementia-related consent issues.
Medical, ethical and legal requirements for the ability to give consent will be systematically incorporated into the development process through accompanying consultations and feedback on item formulations.

Phase 2 – Neurobiological markers of impaired capacity to consent

Phase 2 of the DECISION project will investigate whether plasma-based neurobiological early warning signs ('red flags') can be identified that are associated with impaired capacity to consent in people with cognitive impairments. The aim is to develop a biomarker-based stratification for the early detection of cognitive and functional impairments.

Plasma-based biomarkers
The focus is on low-threshold, laboratory-based methods that can also be used in outpatient settings and without complex diagnostic equipment. The following biomarkers, which are currently being investigated in connection with neurodegenerative processes, are being examined: (23)

- Amyloid pathology: plasma levels of Aβ1-42/1-40
- Tau pathology: phosphorylated tau (pTau217)
- Neurodegeneration: neurofilament light chain (NfL)
- Glial activation (GFAP) as a marker for later stages of the disease
- Apolipoprotein E4: high correlation with the genetic ApoE4 genotype and thus an indirect, non-invasive risk marker for faster progression

These markers are correlated with specific functional impairments – particularly in the areas of judgement, insight into illness, decision-making behaviour and other dimensions that are mapped by the modular test battery.

Magnetic resonance imaging

The aim of the imaging-related part of the project is to identify biologically plausible risk constellations associated with impaired capacity to give informed consent in people with cognitive impairments.

The following will be systematically investigated:
Temporomesial atrophy as a marker of progressive memory impairment,
Vascular lesions as an indication of subcortical dysfunction and executive impairments,
Structural and functional changes in prefrontal and temporoparietal networks that are essential for insight, judgement and decision-making behaviour.

Optical coherence tomography (OCT)

As part of the study, structural and functional markers of neurodegeneration will be recorded using optical coherence tomography (OCT) in cooperation with the Department of Ophthalmology. A comprehensive ophthalmological examination will be performed. It includes slit lamp biomicroscopy, fundoscopy, Goldmann applanation tonometry and best-corrected visual acuity (BCVA) using the standard ETDRS chart at a testing distance of four meters. An SD-OCT system (Spectralis®; Heidelberg Engineering GmbH, Heidelberg, Germany) is used for B-scan acquisition. The peripapillary retinal nerve fiber layer (pRNFL) will be measured with activated eye tracker using ring scans around the optic nerve head (12°, resolution: 768 A-scans, 496 pixels [Z], 57 ⩽ ART ⩽ 100) or the most inner ring of a star-and-ring scan around the optic nerve (12° , resolution: 768 A-scans, 496 pixels [Z], 57 ⩽ ART ⩽ 100). The volume data for the ganglion cell layer (GCL) and inner plexiform layer (IPL) will be calculated as a 3 mm diameter cylinder centered to the fovea derived from a macular volume scan (20° × 20° [5.9 × 5.9 mm], 49 horizontal B-scans, resolution: 512 pixels [X] × 496 pixels [Z], 18 ⩽ ART ⩽ 30).
and retinal pulsatility as a marker of vascular dysfunction, using Doppler-based techniques such as phase-resolved Doppler OCT (?hat Bene etwas dazu gesagt, habe noch nie davon gehört) Via optical coherence tomography angiography (OCT-A) ocular blood flow will be assessed. Structural imaging will focus on macular and peripapillary regions, while functional parameters will be assessed in the fovea centralis. This approach builds on previous work combining OCT and electrophysiological markers in psychiatric populations (24) and is further motivated by evidence linking Alzheimer's disease and glaucoma via shared mechanisms such as impaired glymphatic clearance and disturbed CSF dynamics. (25) Combined imaging and pressure assessment is expected to provide novel insights into the retina as a potential window into central nervous system pathology.

Laboratory tests

To rule out alternative, potentially treatable causes of optic atrophy, a standardized laboratory screening will be conducted. This will include serum levels of vitamin B12 and folate (to exclude nutritional optic neuropathy), inflammatory markers (CRP, ESR) to detect systemic or autoimmune inflammation, and syphilis serology (TPHA/FTA-ABS) to rule out infectious causes. In participants showing atypical clinical features or progressive visual loss, extended laboratory testing will be performed, including vitamin B1 and copper levels, Borrelia serology, and HIV testing, depending on clinical context and risk factors. Evtl. Syphilis, ACE, IL-2, ANA, ANCA, Borrelia, Toxoplasmose eher auch in das extended workup, da sehr selten und meist nur bei entsprechender Anamnese/Klinik.

Clinical examination

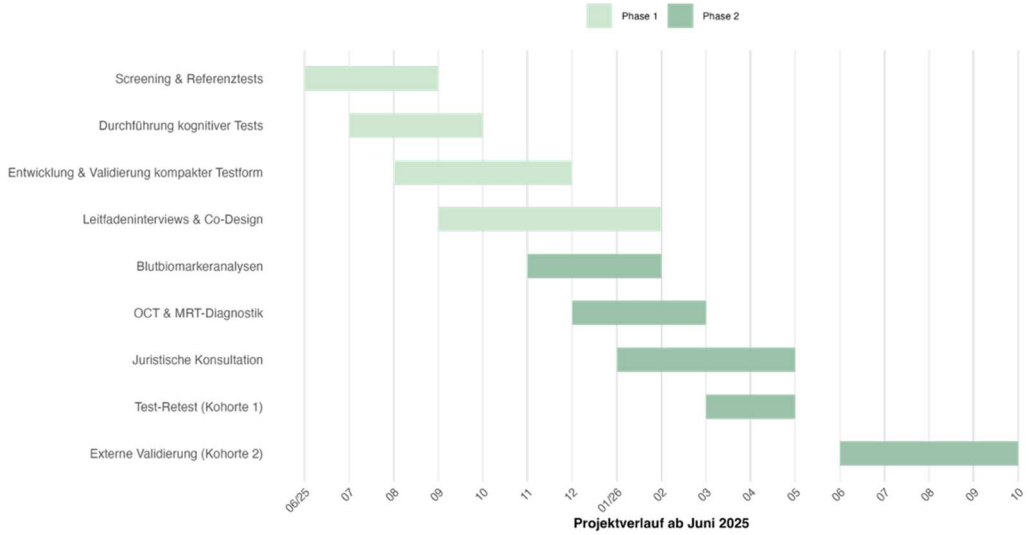
Clinical diagnoses will be established according to ICD-10 criteria, based on a comprehensive assessment. This will include a standardized medical history and clinical examination, supported by relevant laboratory testing to rule out differential diagnoses (e.g., vitamin deficiencies, inflammation, infection). To assess neuropsychiatric comorbidity, all participants will complete a standardized depression questionnaire (e.g., Geriatric Depression Scale or Beck Depression Inventory), and cardiovascular risk factors will be evaluated using a validated cardiovascular risk score (e.g., Framingham Risk Score or SCORE2), as vascular comorbidity may influence optic nerve integrity and cognitive decline. These diagnostic components will ensure a well-characterized study population and allow for appropriate control of confounding factors in the analysis.

To minimise participant burden, individuals will be contacted on only two occasions. During the first contact, they will complete a short cognitive test battery (approx. 15 minutes), including measures of attention, executive function, and language. After a shortened version of this battery has been derived, participants will complete the revised version in a second session, which is expected to take no more than 10 minutes. In addition, the MacCAT-T and CDR will be administered (approx. 25 and 30–60 minutes, respectively) to validate the newly developed short version against established instruments.

Ability of the participants to give consent

Participants' capacity to consent will be assessed at the time of enrolment using proven and standardised procedures as described in the protocol (e.g. MacCAT-T). In the event that a participant loses capacity during the course of the study, it must be ensured that the consent of the legal guardian or authorised representative is obtained. This person must be authorised to make decisions on health matters.

Figure 1 : Overview of the study processes



Study-related burden and risks

For this study, former participants of the in-house AmyClear and ActiGlia trials, who have previously consented to be re-contacted, have caregivers, and are well-characterized, will be re-contacted. These participants, as individuals with Alzheimer's disease, are at the highest risk of losing their capacity to consent over time. To address this, each participant's consent capacity will be reassessed using the MacArthur Competence Assessment Tool (MacCAT-T)at every stage of the study. Existing data including blood samples will be used if participants are no longer able to give informed consent or have borderline capacity. In such cases, only non-invasive measures such as cognitive tests and questionnaires will be conducted, subject to the additional consent of a legally authorized carer.
This approach minimises invasive procedures and reduces the burden on participants, while ensuring the ethical inclusion of people with limited capacity. It balances the need for robust scientific data with a strong commitment to the welfare of participants, and respects autonomy by relying on prior consent and carer supervision. Although the reliance on existing samples limits opportunities for the collection of new biomarkers, this approach prioritises ethical integrity and is consistent with the study's goals of optimising consent assessment thresholds.

Risks of Blood draws

Risk of drawing blood consist in damage of skin, surrounding tissue and nerves and are considered to be minimal. Chronic pain, infections, tissue necrosis, hematoma, edema, scars and sensory complaints and palsy are possible and chronic but rare complications of blood drawing.

Potential burden on the participants

From a psychological perspective, the mental burden experienced by the participants is considered to be low. A questionnaire can be completed at home. Among other things, to keep the burden minimal, the test instruments to be completed are distributed over two days, so that the time required for the first session in the clinic is a maximum of 40 minutes, and for the second session, it is a maximum of 60 to 90 minutes. OCT imaging does not expose patients to radiation.

Information and transparency
Participants must be comprehensively informed in advance about the objective, process, potential burdens and risks as well as how the results will be handled. A focus should be placed on comprehensible, accessible information in simple language.

Privacy concerns
Every digital application has the potential to compromise privacy. Privacy concerns regarding data regarding the data storage and security breaches could also pose risks, especially if personal data is involved. Since no personal information is entered into the digital application, we consider this risk to be low. We use servers located in the European Union that comply with European privacy laws.

Informed consent and project ethics
Weighing up possible risks and scientific meaning this study seems ethically legitimated if participants provide written consent. The risk of physical hazard seems very low. We anticipate that the potential data protection risks to project participants are only minimal, as no identifiable data will be exchanged or stored. The patients´ information sheet is added to this application. Any exchange of data will be in a non-identifiable fashion to fully protect the anonymity and identity of the participants.

Legal and ethical framework
The study is based on the ethical principles of the Declaration of Helsinki as well as the general provisions of the German Civil Code (BGB) and guardianship law. Although Germany has not yet ratified the Convention on Human Rights and Biomedicine, Articles 16 and 17 provide guidelines for the design of ethically acceptable studies. Group-related benefits and the preservation of autonomy take centre stage here.

Benefit
Participants will benefit from personalized feedback on their results, access to educational materials, and insights into their decision-making abilities. Their involvement directly contributes to improving future healthcare and decision-making evaluations, providing both group and potential individual benefits. Participants may also receive access to counseling resources, small compensation, or referrals to appropriate care if needed.

Dealing with relevant results
If the analysis provides biomarkers or other results of clinical relevance, participants must be informed of this if they have agreed to be contacted during the consent process. An appropriate counselling process must be ensured for the disclosure of this information, which also includes the communication of necessary measures or treatment options.

Expected results

- Association between a newly developed, low-effort test battery and the Mac-CAT-T in reliably assessing decision-making capacity
- Link between vascular changes and reduced capacity to consent, independent of the dementia subtype

- Relationship between lesions in key cognitive regions (e.g., attention, language comprehension, information processing) and impaired decision-making capacity, regardless of the underlying condition

Clinical Work-up

Dementia diagnostics will be performed following the standard diagnostic work-up of the Alzheimer Therapie- und Forschungszentrum, which includes psychometric tests, neuroimaging, clinical evaluation, and, depending on medical indication, cerebrospinal fluid biomarkers and positron emission tomography scans. Blood drawing and clock drawing test will be the only study-related procedures that will be additionally introduced and it will take 5 to 10 minutes to complete.

Setting

Alzheimer Therapie- und Forschungszentrum – University Hospital, LMU Munich

Duration of the study

09/2025 – 03/2027

Use of Existing Data for Correlational Analyses

Participants from the AmyClear and ActiGlia studies (project numbers 17-755, 17-569, 18-606), who have already undergone extensive diagnostic work-ups—including CSF analysis and PET imaging—will be recontacted. With the participants' explicit consent, these existing data will be reused to avoid unnecessary repetition of invasive procedures such as lumbar puncture or PET scans. This reuse is essential for the accuracy of clinical classification within the Alzheimer's continuum and reflects our ethical obligation to minimize participant burden. We therefore request that participants provide specific consent to the reuse of previously collected imaging and biomarker data (CSF, PET) for the DECISION study.

Data management and protection

The protection of sensitive patient data must be strictly guaranteed. Data processing is pseudonymised and in accordance with the applicable data protection regulations. To maintain participant confidentiality, each participant will be assigned a unique participant identifier (consecutive number) by the study coordinator upon enrolment, which will be used for all subsequent data analysis and reporting. The participants' personal details (e.g. name and contact data) will be stored in a separate database in a secure encrypted environment, not connected to the internet. All personal information will be destroyed immediately after the completion of the study, unless the participant explicitly agrees to be contacted for future related research, in which case the personal information will be stored for up to 5 years after study completion. Only the study coordinator and principal investigator have access to the personal information. De-pseudonymization would only be permissible in case of significant participant safety concerns. All involved parties will ensure protection of participant personal data and will not include participant names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with regulations, participants will be informed about data handling procedures.

All study data will be stored and processed within the Medical Data Integration Center (MeDICLMU) at LMU University Hospital. MeDICLMU is part of the nationwide Medical Informatics Initiative and provides the technical and organizational infrastructure for secure, GDPR-compliant integration and exchange of clinical and research data across institutions. Data processing will be conducted in a pseudonymized manner in accordance with applicable data protection regulations. The use of participant data for scientific purposes, including correlational analyses, is explicitly outlined in the informed consent form.

Requests for data access within the scope of scientific research are subject to review by the LMU Hospital's Use & Access Committee (UAC).

Contact: *uac@med.uni-muenchen.de*

This infrastructure ensures the secure, transparent, and ethically responsible use of sensitive health data in medical research.

Summary

The proposed study meets the essential criteria for ethically acceptable research. The benefits of the study, both at the individual and group level, outweigh the potential risks, provided that the above measures are consistently implemented. In particular, the review of the capacity to give consent and the information provided to participants in the event of clinically relevant results strengthen the ethical basis of the project. The framework of the study has been developed in close dialogue with the ethics committee.

Signatures of investigators

Principle Investigator Dr. med. Carolin Kurz

Principle Investigator Paulina Tegethoff

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