Project No. 964220

Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment

Deliverable 5.1

Clinical study dossier (Clinical study protocol, Informed Consent Form)

WP 5 – Clinical implementation of the AI-Mind Connector and AI-Mind Predictor

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Revision History

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Abbreviations

AChEI	Acetylcholinesterase inhibitor
AI	Artificial Intelligence
APOE	Apolipoprotein E polymorphism
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDR	Clinical Dementia Rating
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTU	Clinical Trial Unit
DPO	Data Protection Officer
DTA	Data Transfer Agreement
EC	European Commission
EEG	Electroencephalography
EU	European Union
fMRI	Functional magnetic resonance imaging
FPFV	First Patient First Visit

FPLV	First Patient Last Visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
H2020	Horizon 2020
ICH	International Conference on Harmonisation
IVDR	In Vitro Diagnostic Medical Devices Regulation
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
MCI	Mild Cognitive Impairment
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MEG	Magnetoencephalography
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NEM	Nasjonale Forskningsetiske Komité for Medisin og Helsefag
NIA-AA	National Institute on Aging - Alzheimer's Association
PET	Positron Emission Tomography
PI	Principal Investigator
REK	Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk
SOA	State of Art
SPECT	Single photon-emission computed tomography
SSD	Services for Sensitive Data
TSD	Tjenester for Sensitive Data (in Norwegian: Services for Sensitive Data)
UiO	Universitetet I Oslo (in Norwegian: University of Oslo)
WP	Work Package

Partner Short Names

OUS	Oslo University Hospital
accelCH	accelopment Schweiz AG
AE	Alzheimer Europe
Brainsymph	BrainSymph AS
DNV	Det Norske Veritas
HUH	Helsinki University Hospital

IRCCS	Scientific Institute for Research, Hospitalization and Healthcare, San Raffaele Roma
Neuroconnect	Neuroconnect Srl
TLU	Tallin University
UCM	Complutense University of Madrid
UCSC	Università Cattolica del Sacro Cuore

Definitions

Anonymisation	*the process by which personal data is irreversibly altered/anonymised in such a way that a data subject can no longer be identified directly or indirectly, either by the data controller alone or in collaboration with any other party.*
Biometric data	*personal data resulting from specific technical processing relating to the physical, physiological or behavioural characteristics of a natural person, which allow or confirm the unique identification of that natural person (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).*
Consent	*means any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).*
CANTAB	*computerised neuropsychological testing (Cambridge Neuropsychological Test Automated Battery).*
Genetic data	*personal data relating to the inherited or acquired genetic characteristics of a natural person providing unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).*
Personal Data	*any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).*
Processing	*any operation or set of operations which is performed on personal data or on sets of personal data, whether or not by automated means, such as collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).*
Processor	*a natural or legal person, public authority, agency, or other body which processes personal data on behalf of the controller (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).*
Profiling	*any form of automated processing of personal data consisting of the use of personal data to evaluate certain personal aspects relating to a natural person, in particular to analyse or*

	predict aspects concerning that natural person's performance at work, economic situation, health, personal preferences, interests, reliability, behaviour, location or movements (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4).
Prospective Data	*data collected from participants enrolled in the AI-Mind clinical study. Data from 1000 MCI subjects, who will undergo multiple (four times over two years) MEG, EEG and CANTAB testing, and once genetic (APOE4) and P-tau 181 tests, during the project.*
Pseudonymisation	*the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational security measures to ensure that the personal data are not attributed to an identified or identifiable natural person (The European Parliament and the Council of the European Union. General Data Protection Regulation - article 4)*
Retrospective Data	*data originating from multiple data controllers, which can be shared beyond the scope of the original project they were collected for, based on the subjects' informed consent. In AI-Mind, retrospective data will be shared by four of the five clinical partners (excluding HUS).*
TSD Platform	*Centralised secure database provisioned in TSD (located at the University of Oslo, Norway), where AI-Mind data will be collated and processed.*

1 Executive Summary

The aim of WP5 is to collect standardised, prospective data in order to validate and refine the final AI-Mind Connector and AI-Mind Predictor tools. The data will be collected through a clinical study that will recruit people with Mild Cognitive Impairment (MCI). The study will be implemented in five clinical sites in Finland (HUS), Italy (IRCCS/UCSC), Norway (OUS), and Spain (UCM).

1.1 Purpose and Scope of the Deliverable

Deliverable 5.1 is part of task 5.1: "Preparation and implementation of the observational study". AI-Mind's clinical study will recruit people with symptoms of MCI to collect medical data that will be used for the development of the AI algorithms and the validation of the AI-Mind Connector and Predictor tools.

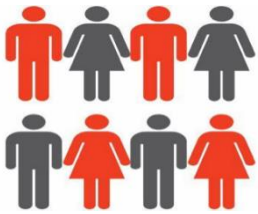
This deliverable provides information about the clinical study dossier, more specifically about the background and standardised clinical procedures, according to which the clinical study will be implemented. The outcomes of the deliverable are based on a process of employed methodologies used to make the enrolment, procedures, and administration of all tests homogeneous among the participating clinical sites.

1.2 Outcomes

The main outcomes regarding the Clinical Study Dossier and clinical study procedures are summarised below.

Inclusion and exclusion criteria

The definition of inclusion and exclusion criteria is based on an extensive literature review and the internal AI-Mind partners` agreement to adhere to the project's objectives.



Definition of MCI at enrolment

General consensus of the criteria to define MCI for the clinical study participants. The inclusion criteria define the degree of cognitive impairment and a minimum of test assessments (table 2).

Ethical requirements and Informed Consent before enrolment

All clinical sites followed the local ethical procedures in alignment with relevant national and EU laws and regulations. An independent AI-Mind ethics advisor has been appointed. Feedback from the user representing association Alzheimer Europe has been implemented.

Ethical Committee approvals

The study has been approved by the Ethical Committees of all clinical sites in due course. The final consensus of the used clinical guidelines, procedures and formation have been incorporated into the application. All Informed Consents have been approved.

Definition of demographic and clinical data collection

Various clinical variables (e.g. demographics, weight, etc.), information about well documented associated pathologies and interventions will be collected. These data will be analysed in order to determine their influence on the risk of progression to dementia for population with MCI.

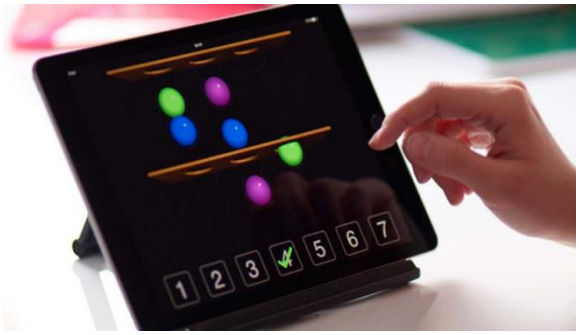
Blood sample collection, storage and shipment

Blood samples will be collected at the first visit, to determine their APOE allele constellation and individual P-Tau associated P181 and/or P217 protein levels. The samples will be collected, stored and shipped according to standardised procedures (Deliverable 2.1).

Harmonisation of EEG recording and storage

All technological aspects for the EEG recording have been standardised and agreed on among the experts from the five clinical sites. All sites will use identical 128-channel EEG devices and harmonised recording parameters (amplification, sampling rate, filters, artefact recognition, duration of each session etc). The characteristics of the recording environment (baseline noise/light brightness) have been standardised (Deliverable 2.1).

Digitalised Cognitive Testing (CANTAB)
All clinical sites will use standardised digital cognitive tests (CANTAB). The tests will be digitally administered in all national languages by electronic tablets (iPads), provided to the participants during the study visits.



2 Introduction

AI-Mind is a five-year EU funded (Horizon2020) project aiming to deliver innovative solutions that will support the definition and diagnosis of the risk to progress to dementia for people who are at the onset of cognitive impairment. The objective is to create an AI-supported cloud-based diagnostic platform that integrates non-invasive, widely available and low-cost state-of-the-art (SOA) technologies. The two integrated AI-Mind tools - Connector and Predictor - will improve and advance the early risk detection to progress to dementia for people affected by Mild Cognitive Impairment (MCI).

In AI-Mind Connector the main objective is to detect synaptic dysfunctions by empowered EEG-based analysis of functional network maps, using AI algorithms. The AI-Mind Connector outcome will be further enriched with other markers of progression to dementia, i.e. blood biomarkers, genetic risk assessment, and computerised cognitive testing, resulting in a second tool, the AI-Mind Predictor, that will finally estimate the risk for progression to dementia for people with MCI.

2.1 WP5 and Deliverable 5.1

The objective of WP5 is to implement and validate AI-Mind Connector and Predictor. This will be achieved through a clinical study that will take place in five European clinical sites: HUS (Finland), IRCCS and UCSC (Italy), OUS (Norway), and UCM (Spain). The collected prospective data (in addition to the classical SOA clinical procedures), will be transferred and analysed on the SSD (Services for Sensitive Data) server at the University of Oslo (UiO – the server is specifically called TSD, according to the translation of SSD in Norwegian).

In the Deliverable 5.1 (Clinical Study Dossier) the following elements and procedures are defined:

- Clinical study overview
- Definition of inclusion and exclusion criteria
- Inclusion process and data collection (including textual data)
- EEG recordings
- Blood sample collection, storage and shipment
- Digital Cognitive testing (CANTAB)
- Harmonisation procedures, deployed to achieve a uniform study implementation to all clinical sites
- Ethical principles and procedures in clinical sites.

3 Clinical Study

3.1 Summary

The aim of this observational, naturalistic study is to validate AI-based tools used for an innovative approach to early dementia risk estimation.

Today, we know that about 50% of patients with MCI are at risk of developing dementia. Early risk signs include functional brain network disturbances as an expression of synaptic dysfunction/failure in the earliest course of potential dementia development. This synaptic dysfunction can be explored by electrophysiological brain signals. The AI-Mind Connector algorithm will identify such functional brain networks in an automated manner using the Graph theory, among other mathematical possibilities. Classical machine and deep learning approaches of artificial intelligence will be deployed by automating these brain network identifications. The AI-Mind Predictor will serve as an enriched Connector, by applying prospectively data from a sample of 1000 MCI participants in a multimodal prediction method for risk estimation. Enrichment is achieved by including digital cognitive tests, APOE alleles genotyping and plasmatic P-Tau protein level information to develop the AI-Mind Predictor algorithm. The AI-Mind Predictor will discriminate between MCI-prodromal-to-dementia patients and MCI-non-prodromal-to-dementia subjects. The results of the anticipated, highly sensitive AI-Mind Predictor will be compared to state-of-the-art (SOA) approaches.

The new technology will not compete with existing diagnostic tools for dementia (CSF, fMRI, PET, SPECT), because AI-Mind wishes to take its role as an early predictive screening method, increasing the percentage of correctly selected MCI subjects for further invasive or more costly diagnostics, resulting in earlier intervention. Importantly, AI-Mind's new data handling procedures only use existing, well-established, globally accessible and low-cost SOA technologies. With AI-Mind's new data processing approach, the goal is to increase today`s low predictive value (<0.5) of the SOA-based clinical dementia prediction, and proactively select with higher accuracy than before, MCI-prodromal patients for further clinical intervention. Thereby, AI-Mind wishes to contribute to delaying dementia development by detecting the risk at the first visit when symptoms occur.

The cutting-edge of the AI-Mind model development and testing will be done by available retrospective and new prospective data collected at the five clinical centres. The 1000 MCI subjects will be recruited as follows: 250 participants at HUH, OUS, and UCM, and 125 at IRCCS and UCSC. All participants will provide signed Informed Consent before entering the study and will be tested 4 times.

The participants will follow a 2-year AI-Mind protocol in parallel with their usual SOA follow-up visits at each hospital (table 3, Schedule of Activities). The protocol includes 4 repetitive electrophysiological measurements (EEG), 4 digitalised cognitive testing (CANTAB); and at the first visit, blood sample collection for APOE allele genotyping and p-Tau analyses. At two of the clinical sites (HUH and UCM), in a subgroup of participants, additional magnetoencephalography measures (MEG) will be analysed for specific feature extraction for modelling the EEG based AI-Mind Connector technology (see table 1).

3.2 Primary and Secondary Objectives of the Clinical Study

The objectives and endpoints of the observational study in the AI-Mind project are listed in table 1.

Table 1: Main objectives and endpoints of the AI-Mind Clinical Study

Objectives	Endpoints
Primary	
• To validate the AI-Mind Connector as a tool for early brain network connectivity disturbance in at-high-risk MCI subjects. • To validate the AI-Mind Predictor as a diagnostic support tool for dementia risk evaluation.	• AI-Mind Connector with estimated specificity and sensitivity value > 0.9. • AI-Mind Predictor with higher prediction value at 24-month for early dementia risk than current clinical practice. • AI-Mind Predictor with estimated specificity and sensitivity value > 0.9.
Secondary	
• To validate the AI-Mind technology on its economic and social impact on the healthcare sector. • To validate the trustworthiness of the AI-Mind technology towards stakeholders. • To validate the clinical use of CANTAB together with classical NTP. • To validate the accuracy of different M/EEG (connectivity) data features for predicting the risk of dementia.	• Delivery of a health technology assessment report showing increased impact on economic and social aspects of the AI-Mind technology. • Report on the increased clinical value of CANTAB as an assessment tool for clinical evaluation of cognitive function. • Report on the predictive value of different M/EEG connectivity measures and of their combinations in dementia risk assessment.

Potential important results confounding background/demographic parameters will be documented in the clinical study protocol by each clinical centre and investigated by the AI-Mind tool development team (e.g., age, sex, education, medication, lifestyle, medical history).

3.3 Study population

Approximately 1500 MCI subjects will be screened in order to consecutively enrol 1000 participants according to the clinical criteria and assessments presented in table 2. All subjects will be enrolled[1] according to the local mild cognitive symptom and clinical SOA procedures.

[1] *the term "enrolled" refers to a participant's, agreement to participate in a clinical study following completion of the Informed Consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*

Screening procedure

The screening procedure for inclusion in the AI-Mind study consists of two steps:

- *Pre- (self-) screening:* people who express their interest in participating in the AI-Mind study, will be given a screening questionnaire (in local language) targeting memory impairment. This test may be either self-administered (i.e. accessed electronically through an internet link), or administered by a clinician. In both cases the data will be collected through electronic forms (Nettskjema, see chapter 3.6). Only people who report mild symptoms, will be invited for further screening.
- *Professional screening:* Following, the potential participants will be given a local inclusion ID number and will proceed to the control of inclusion and exclusion criteria, as described below. If the subjects qualify for the study, they will be given the AI-Mind participant ID number.

Subjects fulfilling the AI-Mind criteria for MCI - based on the acknowledged criteria by the National Institute on Aging-Alzheimer's Association (NIA-AA) - and meeting the AI-Mind inclusion/exclusion criteria (listed below) will be offered participation in the AI-Mind clinical study. In principle, the clinical identification of MCI is defined by the participant`s cognitive status. The assessment tools include Mini Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR), Instrumental activities of daily living (IADL), and the Petersen/Winblad criteria (Petersen et al., 2004) (table 2).

Table 2: *The criteria used for cognitive evaluation and later potential dementia progression*

MCI Criteria	MCI Assessment	Dementia Progression Assessment
• Cognitive concern reported • Objective evidence of impaired cognitive domain • Persevered independence in functional abilities (ADCS-ADL >70%) • Not demented (cognitive changes do not significantly impede social function or work activities) • (Rule out vascular, other causes) • Longitudinal decline (no lasting more than 3 years period at the enrolment time) • Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM – 5	• CDR = 0.5 • MMSE $\geq$ 25 • Petersen/Winblad criteria, 1.5 SD in 1 or more domain **Additional questionnaires:** • IADL/ADCS-ADL • Montreal cognitive assessment (MoCa, ≥17)	• CDR >0,5 • MMSE $\leq$ 24 • MoCa < 17 • Petersen/Winblad criteria, 2 SD in 1 or more domain • IADL below the limit of 70%

• **Clinical Dementia Rating**: The CDR® Dementia Staging Instrument uses a 5-point scale to characterise six domains of cognitive and functional performance applicable to dementia. The six domains are Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. The rating is done by a semi-structured interview of the tested subject and a reliable informant or collateral source (e.g. a family member) referred to as the CDR® Assessment Protocol. Using the CDR® Scoring Table a subject's level of impairment/dementia is characterized: 0 = Normal, 0.5 = Very Mild Dementia, 1 = Mild Dementia, 2 = Moderate Dementia, 3 = Severe Dementia.

• **Mini Mental State Examination** (MMSE): The MMSE is a brief, quantitative measure of cognitive status. It can be used to screen cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual response to treatment. Measurements of cognitive function include registration (repeating named prompts), attention and calculation, recall, language, ability to follow simple commands and orientation. Score of 24 or more (out of 30) is considered a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment.
• **Montreal Cognitive Assessment** (MoCa): Due to ceiling effects in light MCI cases by the MMSE, the MoCa test will be used as well in assessing people affected by MCI. MoCa is a 30-question test that takes around 10 to 12 minutes to complete. MoCA evaluates cognitive abilities including Orientation, Short term memory/Delayed Recall, Executive Function/Visuospatial Ability, Language Abilities, Abstraction, Animal Naming, Attention and Clock-Drawing Test. Because it tests the executive function, it is considered more sensitive in this regard compared to MMSE.

In addition, the following inclusion and exclusion criteria must be fulfilled to enrol subjects in the study:

Inclusion criteria
- Male and female aged between 60 and 75 years.
- AI-Mind MCI assessment listed in table 2.
- Capable of giving signed Informed Consent, which includes compliance with the requirements and restrictions listed in the Informed Consent and in this protocol.

Exclusion criteria
- AI-Mind dementia criteria listed in table 2.
- History of cerebrovascular disease (i.e., major stroke episodes).
- Alcohol Dependence Scale AUDIT score positive.
- Severe medical disorders associated with cognitive impairment (organ insufficiencies, chronic infections, endocrine disorders) which produce chronic uncompensated failure.
- Severe head trauma with structural brain lesion and/or previous brain surgery.
- Severe mental disorders; Schizophrenia, known Major depression or bipolar disorder.
- Neuroimaging evidence of other potential causes of cognitive decline (e.g. subdural hematoma, brain malignancy, metabolic encephalopathy).
- History of non-brain malignancy < 5 years.
- Recent use of psychotropic drugs including AChEI and Memantine < 3 months.
- Participation in trials with experimental drugs.

The age specification is set between the age of 60 – 75 years at enrolment to avoid increasing confounding factors by age, causing cognitive function loss.
There is a documented dementia uneven prevalence of 2:1 in MCI, affecting females more often than males (The Economist Intelligence Unit Limited, 2017). This epidemiological aspect will be addressed during the AI-Mind AI-tool developments and validation to ensure that relevant gender-associated biomarkers are not omitted. Due to this gender discrepancy, it can be hypothesised that there will be an increased prevalence of female-derived available and prospective data for inclusion, which could result in bias during tool development. Using state of art techniques to mitigate the bias of the AI algorithms development will ensure that the collected data is representative for both genders even though the data might be unbalanced due to the prevalence in female subjects.

Furthermore, unanimously at the General Assembly meeting on the 17th of September 2021, all sites decided to integrate supplemental SOA neuropsychological assessments to pre-screen potential

participants. These evaluations will be administered at each site during recruitment screening, covering different cognitive areas: memory, attention, executive functions, visuospatial skills and language. The scores obtained in these additional neuropsychological assessments will be included in Case Report Forms (CRF, table 3 and Annex I).

***Table 3**: Schedule of Activities*

Procedure	Recruitment screening	Follow-up (weeks/months)				Notes
		T0	T1	T2	T3	
		0	8	16	24	
Informed consent signed	X					
Inclusion and exclusion criteria	X					
Sociodemographic and Anamnestic Data	X					
Clinical history	X					
Somatic and neurological physical examination	X	X	X	X	X	
FFQ (Food frequency questionnaire)		X				
Risk Factors	X	X				
Assessment of Somatic Comorbidity	X	X				
Current Therapy	X	X	X	X	X	
Memory Questionnaire	X	X			X	
AI-Mind MCI criteria, table 3	X					
RAVLT (Rey Auditory Verbal Learning test)		X			X	
ROCF (Rey–Osterrieth complex figure test)		X			X	
Boston Naming Test		X			X	
Category Fluency		X			X	
TMT (A,B,B-A)		X			X	
Letter fluency		X			X	
128 lead EEG		X	X	X	X	
CANTAB – digitalised cognitive assessment		X	X	X	X	
MEG		X			X	only at UCM and HUH
Blood sample collection		X				APOE, P-tau variance

Subgroup for MEG procedure

At UCM and HUH, a minimum of 70 patients per site will be measured with simultaneous M/EEG recordings. The localisation accuracy of MEG will be used for extracting the most relevant features for EEG data analysis.

3.4 Timetable of the Clinical Study

The schedule for study conduct, including timelines for key study milestones within the project timeframe, is presented in *figure 1*.

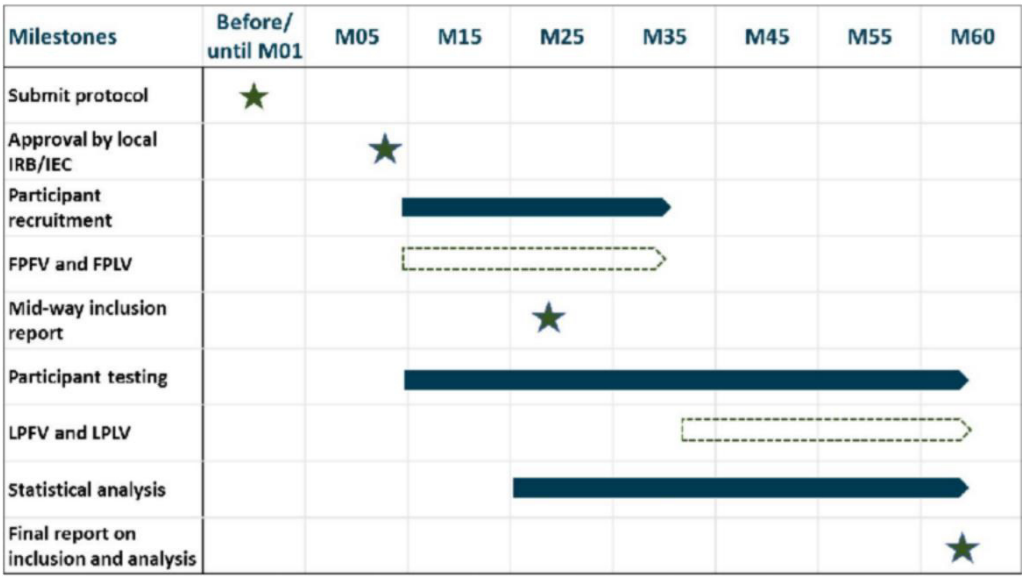


Figure 1: Diagram of the study conduction with key milestones***; FPFV*** *= first patient first visit;* ***FPLV*** *= first patient last visit;* ***LPFV*** *= First patient last visit;* ***LPLV*** *= last patient last visit*

3.5 Informed Consent

Following the EC requirement, the coordinator (OUS) created a Study Information Sheet in English, which included necessary information about the AI-Mind project, including AI-Mind's appointed overall responsible study Data Protection Officer (DPO). This document was used to create each country specific "Informed Consent".

All clinical sites followed their local and national procedures and incorporated the study-specific details provided by the overall "Information Sheet", along with the local requirements from the Ethics Committees. In addition to the national user organisations` input, the Italian sites incorporated in the Informed Consent feedback from Alzheimer Europe and the European Working Group of People with Dementia. An Informed Consent tracking log has been created for each clinical site, to record any potential further amendments to the Informed Consent documents. Informed Consents will be signed and stored in paper form in all sites, except for Norway (OUS). Here the consent is given digitally, complying with the local laws and regulations. All signed documents will be stored according to current local clinical site requirements, following the Personal Data Act/GDPR.
For more details regarding the Informed Consent procedures and the approved documents at each site, refer to Deliverable 9.1.

3.6 Case Report Forms

The Case Report Forms (CRF) are designed to collect all textual information related to initial screening, and, following inclusion, other textual data, e.g. socio-demographic information. All national CRFs are digitally implemented in "Nettskjema" (digitalised web-form) provided by the University of Oslo (UiO). The Nettskjema service transfers the information in a highly secure way directly to the site-specific directories for storage on the TSD server.

Authorised national staff from the clinical sites will enter the data in the electronic form. The delegation of tasks to specific clinical personnel will be done by the Principal Investigators at each clinical site and documented in the "Delegation Log" file (see Deliverable 9.1).

Identification numbers

Two different identification numbers will be used for screening and final inclusion of subjects in AI-Mind:

- *Local inclusion ID:* a local numbering system, selected by each site, to track the potential participant before confirming eligibility to qualify for study participation. The local ID numbers will not be used for data integration on the project`s centralised platform. Each site is responsible for maintaining a list connecting the Local Inclusion ID with the AI-Mind participant ID.
- *AI-Mind participant ID:* when a subject fulfils the inclusion criteria, a unique number will be given, according to the harmonised pseudonymisation process (described in Deliverable 2.1). All nationally collected data will be marked with a unique AI-Mind participant ID, which along with the Site ID and Visit ID, and create a unique Session ID, with which the data entered in the platform will be associated with each participant.

An overview of the electronic CRF forms, the inclusion process, and the use of identification numbers is presented in *figure 2*. The electronic CRF forms may be found in Annex I.

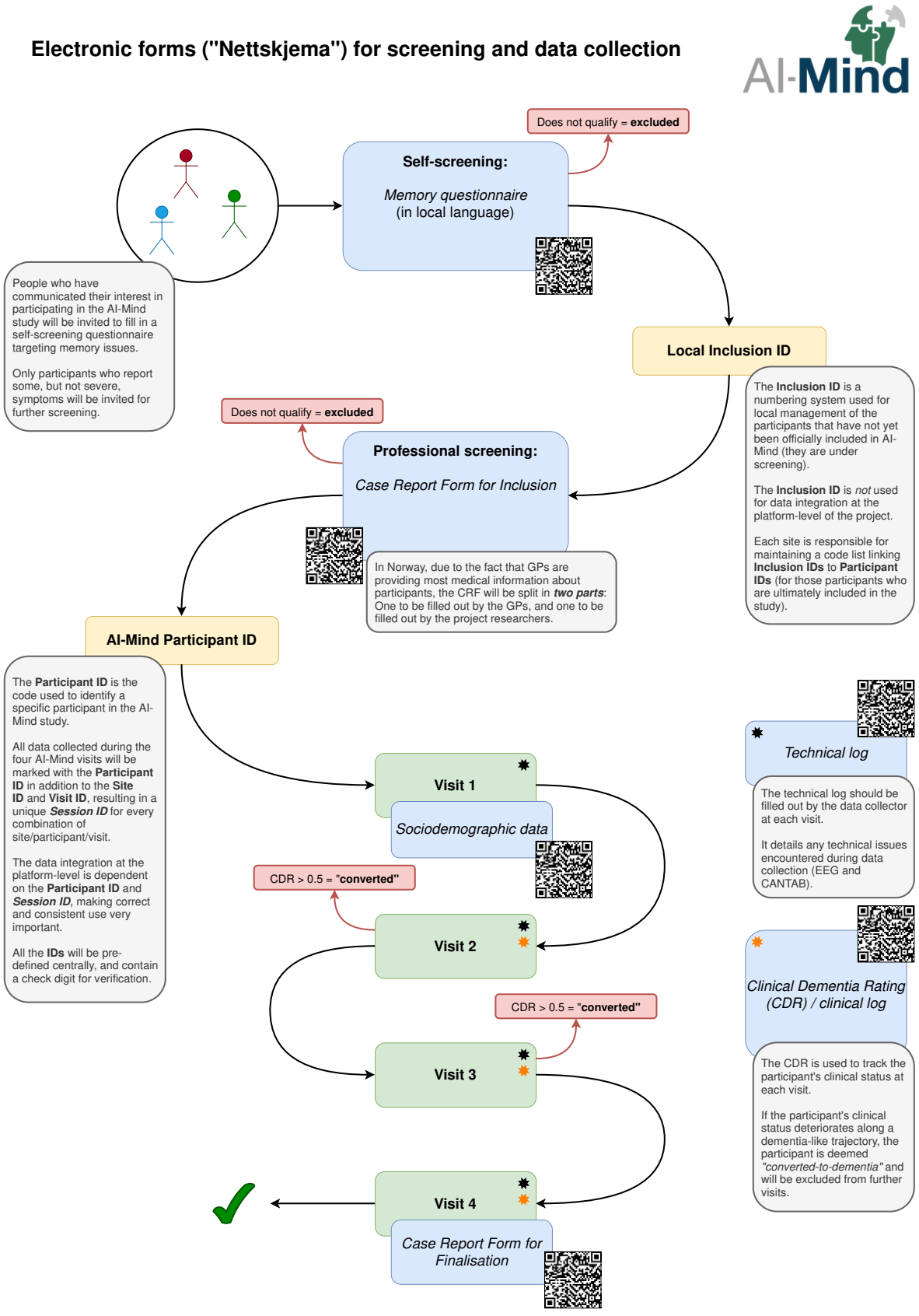


***Figure 2**: Electronic forms for screening and data collection.*

3.7 Instrumental clinical procedures

In this subchapter, the used instrumental clinical procedures are briefly presented. For specific technical details of these procedures, refer to Deliverable 2.1.

Electroencephalography
Empowered EEG recordings will be done at all clinical sites. Resting state (RS) data (three times five-minute intervals; eyes-open, eyes-closed, eyes-open) will be recorded by a 128-channel device, identically procured at all the centres[2]. EEG data will be pre-processed using a semi-automatic pipeline defined in WP2, including SOA procedures for detection and management of signal noise and other artefacts. Moreover, a set of programmed and voluntary reproduced artefacts will be collected at the beginning of each session (harmonised procedures for all clinical centres in order to better identification).

Magnetoencephalography
MEG recordings will be done at two clinical sites: HUS and UCM. MEG recordings will be performed using standard procedures (Gross et al., 2013) with MEGIN systems (306-channel). Data will be collected at a sampling frequency of 2000 Hz and online band-pass filtered between 0.1 and 660 Hz. The MEG protocol will be identical with the EEG protocol. MEGs will be recorded at two-time points (visits 1 and 4). MEG and EEG measurements are conducted simultaneously.

Genetic and protein analysis
Blood sample for DNA isolation and plasma protein assessment will be collected from participants in the morning of the first visit, with participants non-fasting. Collection, storage, and shipment procedures have been standardised by the "Standard Operating Procedure" authored by the responsible blood analysing partner OUS (see Deliverables 2.1 and 9.4).
Genetic analysis of the ε4 allele of APOE is the strongest genetic risk factor for AD compared to those carrying the more common ε3 allele (Lambert JC, et al., 2009; Corder et al., 1994). The presence of this allele is associated with increased risk for both early-onset and late-onset AD, while allele ε 2 is protective. In the future AI model, the genetic data will be beforehand classified either as increased-risk or not. The determination of phosphorylated form of tau (P- tau 181) may increase the specificity and sensitivity in the detection of AD. Other genetic biomarkers, that may eventually stem from research during the course for the AI-mind project, will be potentially added for further evaluation (besides ApoE and P-Tau 181, -217).

Cambridge Neuropsychological Test Automated Battery (CANTAB)
The digital cognitive assessment (CANTAB) is an innovative cloud-based product that is validated for use on an iPad. The AI-Mind CANTAB data set contains 9 well-validated neuropsychological tests, all administered in the 4 national languages (Norwegian, Spanish, Italian and Finnish). The selected tests are non-language specific and European culture-independent, highly sensitive/specific and suitable for use in a wide-range of cognitively affected MCI population. CANTAB will be carried out at each visit (T0, after 8, 16 and 24 months). Each session lasts for 38 – 45 mins.

Classical NPTs scores from the standard subject follow-up will be collected for the selected CANTAB test validation. The classical NTP test battery includes tests of executive function and behaviour (Trail Making Test, Stroop colour-word test, Frontal Assessment Battery); memory test score (Rey's word list learning immediate and delayed recall; Rey Osterrieth figure immediate and delayed recall),

[2] In principle, the AI-Mind Connector algorithm will later also be applicable for lower number of recording channel systems (32- or 64-channels).

visuospatial function (Copy of Rey's figure) and language tests (Phonological and semantic verbal fluency).

Medical Devices
All medical devices used in this study have been routinely employed in clinical use for several decades, except MEG, which has been used for around twenty years. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the local investigators throughout the clinical investigation and appropriately managed by the management support team of the AI-Mind project.

3.8 Recruitment activities

Several dissemination activities have been conducted to identify possible candidates for participation. The use of media, classical (TV, radio, etc.) and modern social media are selected as first-line field for dissemination activities: interviews have been broadcasted on major social and national channels, newspaper and magazine publications have been carried out spreading information on the project and highlighting inclusion criteria. In addition, material to support recruitment procedures has been created: the project's website for professionals and potential participants (in national languages), flyers, explanatory video etc. Finally, national recruitment resource groups and collaborations have spread information about AI-Mind among general medical practitioners and specialists, raising awareness of the project`s objectives and goals.

4 Harmonisation of study procedures

The following study procedure harmonisation meetings took place before the submission of this deliverable:

- *15 April 2021*: "*Define minimum data set of neuropsychological investigations and pathological cut-off limits in each nation. Create the agendas and schedule the harmonisation meetings*".
  In addition, the dissemination activities were discussed. Caregiver associations will be involved to disseminate the project among the potential participants. Clinical partners were asked to provide examples of materials for dissemination.
- *23 June 2021*: clinical expert consensus meeting targeting the definition of inclusion and exclusion criteria. The WP5 leader asked each site to document which cognitive scales are routinely used and to which clinical variables would be considered essential to register in AI-Mind for designing the CRF.
- *28 September 2021*: EEG/Blood sample analysis harmonisation meeting. Standards for EEG recordings had been set. A video for the reproduction of the most frequent movement artefacts had been prepared and shared with the partners. The video was delivered by IRCCS and UCSC. OUS presented the blood sample collection and shipment procedures and will share an educational video on the same topic before the beginning of study enrolment (blood sample collection and processing, samples storage and shipment).

In addition, a cross-WP meeting (breakout session WP2 & 5) took place within the frame of the 3rd General Assembly (Oslo, 17 September 2021). The outcome of the meeting was the final agreement on the previously discussed clinical criteria, neuropsychological assessment proposals for screening and recruitment strategies. Furthermore, as mentioned earlier (chapter 3.7) the classical neuropsychological investigation for comparison and validation of the digitalised CANTAB testing was negotiated and standardised.

5 Statistical aspects and power calculation

It is assumed that AI-Mind Predictor will achieve specificity and sensitivity > 0.9 in the targeted population, in which the approximate prevalence of both 'prodromal-to-dementia' and 'non-prodromal-to-dementia' is about 50%. We explored the sample size required for the ability to verify the measures of the predictive performance, i.e. the sizes of both validation and test data sets. The sample size calculations have been carried out for the specificity and sensitivity estimates by simulating the appliance of the binary classifier to a simulated dataset of total N subjects, fixing the performance of the classifier to specificity = sensitivity = 0.9, as the lower bound case will result in largest variability of the results. Due to symmetry caused by the equal prevalence of prodromal/non-prodromal and specificity = sensitivity, and the confidence intervals will be equal for sensitivity and specificity estimators. The width of the (1 - α)-confidence interval of the estimated classifier sensitivity and specificity is used to determine the accuracy of the estimates given sample size N. One thousand participants and 4000 repetitive measurements had been calculated as sufficient for reaching the AI-Mind goal to achieve a specificity and sensitivity > 0.9. Furthermore, the definition for each participant analysis set should be defined at the participant level. To implement the estimated framework, defined analysis data sets will be defined (table 4) that specify the set of data used in the analysis for a given estimate (or family of estimates that differ only in endpoint) based on how key intercurrent events will be handled for that estimate. For these purposes of analysis, the following analysis sets have been defined:

***Table 4**: Defined analysis data sets*

Defined Analysis Data Sets	*Description*
Training set	Participants not included in the test set and randomised to the model building set.
Validation set	Participants not included in the test set and randomised to the model validation set.
Test set	Participants randomised to the model performance verification set and will not be used inmodel building.

Multivariate classifier methods such as multivariate logistic regression will be used to predict the binary outcome of subjects. The statistical analysis plan will describe the planned analyses in greater detail (WP3). The statistical analysis plan will include a more technical and detailed description of the statistical analyses (future WP3 deliverables).

➢ Participants lost to follow up and dropped out

A participant will be considered lost to follow-up if he/she repeatedly fails to show up to scheduled visits and is unable to be contacted by the study site. If a participant fails to appear at the clinic for a scheduled study visit, the following must occur:

- The site personnel will attempt to contact the participant and reschedule the missed visit as soon as possible. The participant will be counselled on the importance of maintaining the visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study (lost to follow-up).

In addition, if the participant during the 2-year follow-up develops criteria for exclusion, he/she will be informed and leave the study (drop-out).

6 Regulatory status and ethical activities

The study will be conducted according to the Declaration of Helsinki, Institutional Review Boards (21 CFR 56), Obligations of Clinical investigators (21 CFR 312) and Council for International Organizations of Medical Sciences International Ethical Guidelines (CIOMS). In addition, all clinical sites will comply with Good Clinical Practice guidelines and applicable laws and regulations.

All study records will be kept on the secure TSD server, administered by the University of Oslo, operating in accordance with the EU Data Protection Directive 95l46lEC and the General Data Protection Regulation (GDPR). The code sheets linking a patient's name to a patient identification number will be stored separately at each clinical site in each participating nation on a secure local data server. The final repository (UiO) has been approved by the local ethical committees, along with the terms of data storing (time, privileges, etc.). All nationally approved data transfers have been negotiated and documented in a Data Transfer Agreement (DTA), signed between OUS and the clinical sites (HUS, IRCCS, UCSC, UCM). All national clinical sites must comply with all applicable privacy regulations, health insurance regulations, EU Data Protection Directive 95l46lEC and the General Data Protection Regulation (GDPR).

To address the specific ethical and legal concerns on data safety and privacy in the project, seven partners in our consortium (AE, DNV, OUS, HUH, IRCCS, UCSC and TLU) have been ensuring that the AI-Mind service is in line with all applicable European and national standards and legislation. In addition, the project is supervised by the independent Ethics Advisor (Deliverable 9.5), underlining the commitment to address legal and ethical concerns regarding the introduction of AI-based supportive medical diagnostics. We will ensure that governance requirements for data sharing support the development of the, hopefully, trustworthy AI-Mind solutions.

Throughout the project lifecycle, we will provide continuous governance and assurance for data sharing relating to quality, security, trust and transparency. The requirements and current barriers for cross-border sharing of prospective data to support a future European AI supportive diagnostic decision-making tool have been addressed. The study design and administration are in line with existing European and international regulations (WP1). The goal is to create governance and assurance frameworks that will support data sharing in a trusted, safe and sustainable manner (see Deliverable 1.3). Additionally, to be able to fully achieve the expected impact of the project, potential future legal barriers for implementing the AI-tools in a clinical setting have been and will be continuously addressed.

Amongst others, legal and socio-ethical assessments have to consider issues related to liability and accountability for the tools' performance, general health law requirements, patient rights, and regulations regarding medical devices and the processing of personal data.

6.1 Relevant guidance documents

The following guidelines, scientific and legal papers have been used when designing the AI-Mind project (table 5).

Table 5: *Relevant guidelines corresponding to Important project areas*

Scientific areas	Relevant guidelines or articles

*Good clinical practice**	Guideline for good clinical practice E6(R2), 23 July 2015 EMA/CHMP/ICH/135/1995 Committee for Human Medicinal Products Step 2b.
Statistical principles for clinical trials	ICH Topic E 9 Statistical Principles for Clinical Trials.
Best practice of treatments / standard-of-care on MCI patients (or dementia patients)	Albert, M.S et al. "The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease". Alzheimer's & Dementia, 2011.
Clinical recommendation on psychiatric disorders.	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), 2013, American Psychiatric Association (APA).
Good Clinical Practice on EEG procedures	• Seeck, M et al. "The standardised EEG electrode array of the IFCN", 2017, Clinical Neurophysiology. • Rossini et al. "Methods for analysis of brain connectivity: An IFCN-sponsored review", 2019, Clinical Neurophysiology.
Good Clinical Practice on MEG procedures	Gross et al., "Good practice for conducting and reporting MEG research", 2013, Neuroimage.
Good Clinical Practice on genetic testing of APOE polymorphism	Zhong, Li et al. "A rapid and cost-effective method for genotyping apolipoprotein E gene polymorphism", 2016, Mol Neurodegeneration.
Health Technology assessment	**Relevant guidelines or articles**
Health Technology Assessment	EUnetHTA Joint Action 2, Work Package 8. HTA Core Model® version 3.0 (Pdf); 2016. Available From www.htacoremodel.info/BrowseModel.aspx.
Clinical methodology and regulations	**Relevant guidelines or articles**
Data safety and management	• Expert Group on FAIR data, 2018 report: "Turing Fair into Reality, Final report and action plan from the European Commission expert group on FAIR data", Publication Office of EU. • Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
Clinical Evaluation and Performance Evaluation of Medical Device Software	MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software March 2020, by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745

6.2 Scientific advice / protocol assistance

Scientific advice and protocol assistance have been provided by the local Clinical Trial Units (CTU), legal departments and ethics committees. The AI-MIND protocol has been finalised, but amendments may be necessary for the future. The CTUs will assist the local Principal Investigators (PI) with all potential future amendments.

The study has been approved by the Ethical Committees of all clinical sites in due course. The final consensus of the used clinical guidelines, procedures and formation have been incorporated. The approvals given by the clinical sites' Ethical Committees are included in Annex II.

The principles of the local Ethics Committees are described below.

6.2.1 HUH

At HUH, the clinical studies are conducted along the principles of respect for the fundamental and human rights of citizens, on a fully voluntary basis, and in compliance with good research practice. All studies must have been approved by the HUS Ethics Committee and granted a separate research permit by the department/infrastructure the study relates to. HUS Ethics Committees approve the medical research conducted on humans, human embryos, and foetuses in the greater Helsinki region. Clinical trials are an essential part of the research conducted in HUS. The subjects participating in clinical trials are covered by the HUS indemnity insurance and protection on the same grounds as other patients. Any study has to obtain the favourable opinion and permission of the HUS Ethics Committee. An informed consent of the participant has to be given to HUS. Such document is requested and must comply with the European and national finish legal requirements for the protection of the research subjects. In addition, the study must document the necessary resources for carrying it out and cover the costs it incurs on the hospital district. The data protection of confidential data must be safeguarded as required by law, and the code key of the study must be retained in possession of HUS or someone acting on its behalf.

6.2.2 UCSC

The Catholic University Ethics Committee is inspired by the values and founding principles of the Università Cattolica del Sacro Cuore (UCSC). The Ethics Committee aims to be an integrative service to the clinical-assistance work for the achievement of excellence in the care of every person who is a guest and user of the facilities. The principles of the Ethics Committee can be outlined with two main guidelines:

i. to provide a public guarantee of respect for life from conception to its natural end for the health and for the rights of the individuals in the context of clinical practice and research, facilitating, especially in cases of particular difficulty, the choices of caregivers and collaboration with patients in the information-deliberation process
ii. to overcome the fragmentation and complexity of medical specialities by interpreting them as part of the anthropological unity of the human person, and in particular, of the suffering person, with a view to improving the quality of care and research.

The UCSC Ethics Committee has been reconstituted in accordance with the Health Ministry Decree 08/02/2013 (Official Gazette no. 96 of 24/04/2013) which introduced new criteria for the composition and operation of ethics committees.

6.2.3 IRCCS

The Ethics Committee of IRCCS San Raffaele Roma in Via della Pisana is an independent body, established within the Institute and not hierarchically subordinate to it. The Ethics Committee is established by Resolution of the President of the Institute no. 35/13 of 14/11/2013, pursuant to DGR Lazio N. 301 of 03/10/2013, in implementation of the Health Ministry Decree of 8 February 2013, published in G.U. no. 96 of 24/04/2013 "Criteria for the composition and functioning of ethics committees". The IRCCS Ethics Committee is inspired by the respect for human life, with reference to the Italian Constitution, the Charter of Human Rights, the Recommendations of international bodies, national and international medical ethics, the Declaration of Helsinki, the Oviedo Convention, the UN Convention on the Rights of Persons with Disabilities, and the Recommendations, where applicable, of the National Committee for Bioethics (established by Decree of the Presidency of the Council of Ministers of 28/3/1990).
For the execution of clinical trials of medicinal products, the IRCCS Ethics Committee has as its reference in good clinical practice provided by the guidelines of the European Union, agreed upon in the framework of the International Conference on Harmonization (ICH) in the 1996 version and

acknowledged in the Ministry of Health Decree no. 162 of 15/07/1997 (G.U. no. 191 of 18/08/1997) and in the Legislative Decree no. 211 of 24/06/2003 "Implementation of Directive 2001/20/EC on the application of good clinical practice in the execution of clinical trials of medicinal products for clinical use".

6.2.4 OUS

In Norway, there are four Regional Committees for Medical Research Ethics (REK) based on the "Research Ethics Act LOV-2017-04-28-23". The purpose of the act is to ensure that public and private research is conducted in accordance with recognised norms of research ethics. The law is the legal basis for the National Research Ethics Committees. REKs must be professionally independent. The four Regional Ethics Committees are based in Oslo, Bergen, Trondheim and Tromsø. The committee members are appointed by the Ministry of Education and Research for a period of four years. Each committee consists of nine members. The committees are broadly composed of people with different professional backgrounds. The law states that the committees must have competence in relevant research disciplines, ethics and law. Their area of responsibility follows the "Health Research Act LOV-2008-06-20-44" and other legislation that assigns tasks to the committees. This means that medical and health research on humans, human biological material, or health information, and the establishment of research biobanks must have prior approval from REK. REK shall make a general research ethics assessment of the project, and assess whether the project meets the requirements in the "Health Research Act LOV-2008-06-20-44". The "National REK for Medicine and Health Sciences" (NEM) is the appeal body for local REK's decisions. Applications are preferably distributed to REK in the geographical region where the research manager is established. In connection with the Norwegian study at OUS in the AI-Mind project, the approval was given by REK-region South-East.

6.2.5 UCM

The UCM Ethics Committee will ensure compliance with all applicable legal regulations in the development of clinical trials, as well as the ethical standards contained in the Code of Ethics of the General Council of Medical Associations of Spain and those internationally accepted and included in the Declaration of Helsinki in its latest revision and in the Oviedo Convention on human rights and biomedicine, as well as the ICH Guide to Standards of Good Clinical Practice. These are implemented to guarantee the protection of the rights of the subjects, respect their privacy, guarantee the confidentiality of all data, and preserve the accuracy of the results of the clinical trial. The standardised work procedures are prepared in accordance with the provisions of:

i. the Royal Decree 1090/2015, of December 4, which establishes the requirements for conducting clinical trials with drugs, and
ii. Decree 39/1994, of April 28, which regulates the competencies of the Community of Madrid in matters of clinical trials with drugs, and iii. the rules of Good Clinical Practice (CPMP / ICH / 135/95) that will ensure that the data is reliable and that the rights and integrity of the subjects are protected, maintaining the confidentiality of their data.

7 References

- Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B. and Phelps, C.H. (2011), The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7: 270-279. doi:10.1016/j.jalz.2011.03.008.

- American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition (DSM-5), 2013.

- Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell Jr PC, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet. 1994; 7:180–4.

- Cowley, L.E., Farewell, D.M., Maguire, S. et al. Methodological standards for the development and evaluation of clinical prediction rules: a review of the literature. Diagn Progn Res 3, 16 (2019). https://doi.org/10.1186/s41512-019-0060-y.

- Directorate-General for Research and Innovation (European Commission). *Turning FAIR into reality. Final report and action plan from the European Commission expert group on FAIR data*. 2018. https://op.europa.eu/en/publication-detail/-/publication/7769a148-f1f6-11e8-9982-01aa75ed71a1/language-en/format-PDF/source-80611283#.

- EUnetHTA Joint Action 2, Work Package 8. *HTA Core Model® version 3.0 (Pdf)*, 2016. www.htacoremodel.info/BrowseModel.aspx.

- European Medicines Agency. *Guideline for good clinical practice E6(R2)*. 2015, EMA/CHMP/ICH/135/1995 Committee for Human Medicinal Products. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.

- European Medicines Agency. *ICH Topic E 9 Statistical Principles for Clinical Trials*. 1998, CPMP/ICH/363/96. https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials.

- European Union Law. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). 2016. http://data.europa.eu/eli/reg/2016/679/oj

- Gross J, Baillet S, Barnes GR, Henson RN, Hillebrand A, Jensen O, Jerbi K, Litvak V, Maess B, Oostenveld R, Parkkonen L, Taylor JR, van Wassenhove V, Wibral M, Schoffelen JM. Good practice for conducting and reporting MEG research. Neuroimage. 2013 Jan 15;65:349-63. doi: 10.1016/j.neuroimage.2012.10.001. Epub 2012 Oct 6. PMID: 23046981; PMCID: PMC3925794.

- Lambert JC, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009; 41:1094–9. [PubMed: 19734903].

- Medical Device Coordination Group. *MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software*. 2020. https://ec.europa.eu/health/sites/default/files/md_sector/docs/md_mdcg_2020_1_guidance_clinic_eva_md_software_en.pdf.

- Rossini PM, Di Iorio R, Bentivoglio M, Bertini G, Ferreri F, Gerloff C, Ilmoniemi RJ, Miraglia F, Nitsche MA, Pestilli F, Rosanova M, Shirota Y, Tesoriero C, Ugawa Y, Vecchio F, Ziemann U, Hallett M. Methods for

analysis of brain connectivity: An IFCN-sponsored review. Clin Neurophysiol. 2019 Oct;130(10):1833-1858.

- Seeck M., Laurent Koessler, Thomas Bast, Frans Leijten, Christoph Michel, Christoph Baumgartner, Bin He, Sándor Beniczky. The standardized EEG electrode array of the IFCN. Clinical Neurophysiology, Volume 128, Issue 10, 2017, Pages 2070-2077, ISSN 1388 2457,https://doi.org/10.1016/j.clinph.2017.06.254. http://www.sciencedirect.com/science/article/pii/S1388245717304832.

- The Economist Intelligence Unit Limited (2017). *Assessing the socioeconomic impact of Alzheimer's in western Europe and Canada*. https://www.ceafa.es/files/2017/05/Evaluación%20del%20impacto%20socioeconómico%20de%20la%20enfermedad%20de%20Alzheimer%20en%20Europa%20Occidental%20y%20Canadá-1.pdf.

- The European Parliament and the Council of the European Union. *General Data Protection Regulation - article 4 [Internet] via Intersoft Consulting*. Available from: https://gdpr-info.eu/art-4-gdpr/.

- The International Organization for Standardization. *ISO 25237:2017 Health informatics — Pseudonymization [Internet]*. 1st ed. 2017. 62 p. Available from: https://www.iso.org/standard/63553.html.

- Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004 Sep;256(3):240-6. doi: 10.1111/j.1365-2796.2004.01380.x. PMID: 15324367.

- Zhong, Li et al. A rapid and cost-effective method for genotyping apolipoprotein E gene polymorphism. Molecular neurodegeneration vol. 11 2. 12 Jan. 2016, doi:10.1186/s13024-016-0069-4.

Annex I

CRF – Nettskjema

AI-Mind: Case Report Form for Inclusion

Mandatory fields are marked with a star *

Clinician's name and contact information

The name of the project associate filling in the CRF form (first name and surname)? *

Not the participant's name.

What is your e-mail address? *

Not the participant's email.

Page break

Mandatory fields are marked with a star *

Local Inclusion ID

*

The ***Inclusion ID*** is a code used for local management of potential participants *prior* to inclusion into the AI-Mind study. Once the participant is included in the study, they will receive their Participant ID.

Don't know the participant's Inclusion ID? Please contact the clinical site PI.

Page break

Mandatory fields are marked with a star *

INCLUSION CRITERIA CHECKLIST

Age between 60 and 75 years (at the time of inclusion)? *

- ○ Yes
- ○ No

Cognitive concern reported by participant and/or a proxy caregiver? *

- ○ Yes
- ○ No

Objective evidence of impaired cognitive domain (yet preserved independence in functional abilities)? *

- ○ Yes
- ○ No

Not demented; cognitive changes do not significantly impede social function or work activities? *

- ○ Yes
- ○ No

Longitudinal decline (not lasting more than 3 years period at the enrollment time) *

- ○ Yes
- ○ No

DSM-5 diagnosis "MCI" at the time of inclusion? *

- ○ Yes
- ○ No

Are vascular (stroke) or other causes of the cognitive impairment ruled out? *

- ○ Yes
- ○ No

MMSE ≥ 25 or MoCA ≥ 17? *

- ○ Yes
- ○ No

(I)ADL/ADCS-ADL > 70%? *

- ○ Yes
- ○ No

Petersen/Winblad criteria, 1.5 SD in 1 or more domain fulfilled? *

- ○ Yes
- ○ No

CDR ≤ 0.5? *

- ○ Yes
- ○ No

Page break

Mandatory fields are marked with a star *

EXCLUSION CRITERIA CHECKLIST

History of cerebrovascular disease (i.e. major stroke episodes)? *

- ○ Yes
- ○ No

Alcohol Dependence Scale (e.g. AUDIT) score positive? *

- ○ Yes
- ○ No

Any severe medical disorders associated with cognitive impairment (organ insufficiencies, chronic infections, endocrinical disorders) which produce chronic uncompensated insufficiency? *

- ○ Yes
- ○ No

Any severe head trauma with structural brain lesion and/or previous brain surgery? *

- ○ Yes
- ○ No

Any severe mental disorders (e.g. schizophrenia, known major depression or bipolar disorder)? *

- ○ Yes
- ○ No

Any neuroimaging evidence of other potential causes of the cognitive decline (e.g. subdural haematoma, malignancy)? *

- ○ Yes
- ○ No

History of malignancy < 5 years? *

- ○ Yes
- ○ No

Recent use of psychotropic drugs including AChEI and Memantine (< 3 months)? *

- ○ Yes
- ○ No

MMSE ≤ 24 or MoCa < 17? *

- ○ Yes
- ○ No

Petersen/Winblad criteria, 2 SD in 2/3 cognitive domain/according to MCI criteria *

- ○ Yes
- ○ No

Positiv (I)ADL score (retained function) less than 70%? *

- ○ Yes
- ○ No

Page break

Mandatory fields are marked with a star *

ASSESSMENT SCALE RESULTS

Cognitive functioning

Cognitive functioning scale *

*Specify which scale has been used to assess **cognitive functioning**.*

- ○ MMSE
- ○ MoCA
- ○ Other (specify below)

Specify which assessment scale was used to assess cognitive functioning *

ⓘ This element is only shown when the option "Other (specify below)" is selected in the question "Cognitive functioning scale"

Cognitive functioning scale score *

Please enter the score obtained with the assessment scale.

Activities of Daily Living (ADL)

ADL scale *

*Specify which of the **ADL** scales has been used.*

- ○ IADL
- ○ ADL-MCI
- ○ Other (specify below)

Specify which of ADL scales was used *

ⓘ This element is only shown when the option "Other (specify below)" is selected in the question "ADL scale"

ADL scale score *

*Please enter the obtained **positive** ADL score (i.e., the percentage of intact function).*

Clinical Dementia Rating (CDR)

Use the calculator found here to compute the Global Score.

CDR scale Global Score *

Please enter the obtained CDR-Global Score.

Depression

Depression scale *

*Specify which scale has been used to assess **depression**.*

- ○ MADRS
- ○ GDS
- ○ Other (specify below)

Specify which assessment scale was used to assess depression *

ⓘ This element is only shown when the option "Other (specify below)" is selected in the question "Depression scale"

Depression scale score *

Please enter the score obtained with the assessment scale.

Alcohol abuse

Link to online AUDIT screening.

Alcohol abuse scale *

*Specify which scale has been used to assess **alcohol abuse**.*

- ○ AUDIT
- ○ Other (specify below)

Specify which assessment scale was used to assess alcohol abuse *

ⓘ This element is only shown when the option "Other (specify below)" is selected in the question "Alcohol abuse scale"

Alcohol abuse scale score *

Please enter the score obtained with the assessment scale.

Page break

Mandatory fields are marked with a star *

NEUROPSYCHOLOGICAL TEST SCORES

Rey Auditory Verbal Learning Test (RAVLT)

RAVLT: Learning, trial 1

RAVLT: Learning, trial 2

RAVLT: Learning, trial 3

RAVLT: Learning, trial 4

RAVLT: Learning, trial 5

RAVLT: Delayed recall

RAVLT: Recognition

RAVLT: Recognition, false positives

Rey-Osterrieth Complex Figure Test (ROCF)

ROCF: Time used

ROCF: Copy

ROCF: Delayed recall

ROCF: Recognition

Boston Naming Test (BNT)

BNT: Score

Category Fluency (CF)

CF: Total score

CF: Total errors

Trailmaking Test (TMT)

TMT: A

In seconds.

TMT: A, number of errors

TMT: B

In seconds.

TMT: B, number of errors

Letter Fluency (LF)

LF: Letter 1

LF: Letter 2

LF: Letter 3

LF: Total errors

Page break

Mandatory fields are marked with a star *

CLINICAL HISTORY

Months since onset of cognitive symptoms *

Please round up or down to nearest whole month.

Type of symptoms debut *

- [ ] Acute
- [ ] Subacute
- [ ] Insidious
- [ ] Unknown

Checklist of cognitive symptoms

Memory (amnesia)

- [x] No
- [ ] Yes
- [ ] Unknown

Language (anomia, speech trouble)

- [x] No
- [ ] Yes
- [ ] Unknown

Motor programming (apraxia)

- [x] No
- [ ] Yes
- [ ] Unknown

Recognition of objects/faces (agnosia/prosopagnosia)

- [x] No
- [ ] Yes
- [ ] Unknown

Attention

- [x] No
- [ ] Yes

- ○ Unknown

Planning (executive function disorder)

- ◉ No
- ○ Yes
- ○ Unknown

Checklist of other symptoms

Extrapyramidal

- (●) No
- ( ) Yes
- ( ) Unknown

Focal motor

- (●) No
- ( ) Yes
- ( ) Unknown

Falls

- (●) No
- ( ) Yes
- ( ) Unknown

Fluctuations

- (●) No
- ( ) Yes
- ( ) Unknown

Sleep disorders

- (●) No
- ( ) Yes

○ Unknown

Checklist of psychiatric symptoms/behavioural abnormalities

Anxiety

- (●) No
- ( ) Yes
- ( ) Unknown

Depression

- (●) No
- ( ) Yes
- ( ) Unknown

Apathy

- (●) No
- ( ) Yes
- ( ) Unknown

Lack of concern

- (●) No
- ( ) Yes
- ( ) Unknown

Fatuity

- (●) No
- ( ) Yes

- ○ Unknown

Disinhibition

- ◉ No
- ○ Yes
- ○ Unknown

Aggressiveness

- ◉ No
- ○ Yes
- ○ Unknown

Fixed ideas/delusion

- ◉ No
- ○ Yes
- ○ Unknown

Hallucinations

- ◉ No
- ○ Yes
- ○ Unknown

Poor self-care/grooming

- ◉ No

- ○ Yes
- ○ Unknown

Lack of awareness

- ◉ No
- ○ Yes
- ○ Unknown

Page break

Mandatory fields are marked with a star *

SOMATIC AND NEUROLOGICAL PHYSICAL ASSESSMENT

Height *

*Please round up or down to nearest whole **cm**.*

Weight *

*Please round up or down to nearest whole **kg**.*

Abdominal circumference *

*Please round up or down to nearest whole **cm**.*

Blood pressure (systolic)

*In **mmHg**.*

Blood pressure (diastolic)

*In **mmHg**.*

Total cholesterol

If available, please provide a recent value (max. 1 year).

Neurological signs *

Other than cognitive symptoms.

- ○ No
- ○ Yes

Please specify the neurological signs

ⓘ This element is only shown when the option "Yes" is selected in the question "Neurological signs"

Use keywords.

Sleep disorders

- ○ No
- ○ Yes
- ○ Don't know

Burnout or severe stress over time

Is it highly probable that the person's cognitive symptoms are caused by **burnout** or **severe stress over time**?

- ○ No
- ○ Yes
- ○ Don't know

Page break

Mandatory fields are marked with a star *

RISK FACTORS

Dementia

Total number of first-degree relatives with dementia

Include all first-degree relatives with a known dementia condition, both deceased and alive.

Relatives with dementia?

- ○ No
- ○ Yes
- ○ Don't know

Specify the relative who has/had dementia

ⓘ This element is only shown when the option "Yes" is selected in the question "Relatives with dementia?"

Multiple answers may be selected.

- ☐ Mother
- ☐ Father
- ☐ Sister(s)
- ☐ Brother(s)

How many sisters are/were affected by dementia?

ⓘ This element is only shown when the option "Sister(s)" is selected in the question "Specify the relative who has/had dementia"

Please report the total number of sisters

ⓘ This element is only shown when the option "Sister(s)" is selected in the question "Specify the relative who has/had dementia"

*This number should include **both** healthy and those affected by dementia*

How many brothers are/were affected by dementia?

This element is only shown when the option "Brother(s)" is selected in the question "Specify the relative who has/had dementia"

Please report the total number of brothers

This element is only shown when the option "Brother(s)" is selected in the question "Specify the relative who has/had dementia"

*This number should include **both** healthy and those affected by dementia*

Extrapyramidal pathology

Relatives with extrapyramidal pathology?

- ○ No
- ○ Yes
- ○ Don't know

Which relative has/had extrapyramidal pathology?

This element is only shown when the option "Yes" is selected in the question "Relatives with extrapyramidal pathology?"

Multiple answers may be selected.

- ☐ Mother
- ☐ Father
- ☐ Sister(s)
- ☐ Brother(s)

How many sisters are/were affected by extrapyramidal pathology?

This element is only shown when the option "Sister(s)" is selected in the question "Which relative has/had extrapyramidal pathology?"

Please report the total number of sisters

This element is only shown when the option "Sister(s)" is selected in the question "Which relative has/had extrapyramidal pathology?"

*This number should include **both** healthy and those affected by extrapyramidal pathology*

How many brothers are/were affected by extrapyramidal pathology?

This element is only shown when the option "Brother(s)" is selected in the question "Which relative has/had extrapyramidal pathology?"

Please report the total number of brothers

This element is only shown when the option "Brother(s)" is selected in the question "Which relative has/had extrapyramidal pathology?"

*This number should include **both** healthy and those affected by extrapyramidal pathology*

Other

Relatives with psychiatric conditions?

Include severe conditions, such as major depressive disorder, schizophrenia, bipolar disorder, etc.

- ○ No
- ○ Yes
- ○ Don't know

Smoking/tobacco use?

- ○ No, never
- ○ Not currently, but previously
- ○ Yes, currently

Age when started smoking?

This element is only shown when the option "Not currently, but previously" or "Yes, currently" is selected in the question "Smoking/tobacco use?"

Please round up or down to nearest whole year.

Age when quit smoking?

This element is only shown when the option "Not currently, but previously" is selected in the question "Smoking/tobacco use?"

Please round up or down to nearest whole year.

Average number of cigarettes per day?

This element is only shown when the option "Not currently, but previously" or "Yes, currently" is selected in the question "Smoking/tobacco use?"

Substance (other than tobacco or alcohol) use?

Cannabis, cocaine, heroin, etc.

- ○ No, never
- ○ Not currently, but previously
- ○ Yes, currently

Specify substance

This element is only shown when the option "Yes, currently" or "Not currently, but previously" is selected in the question "Substance (other than tobacco or alcohol) use?"

Age when started using the substance?

This element is only shown when the option "Yes, currently" or "Not currently, but previously" is selected in the question "Substance (other than tobacco or alcohol) use?"

Please round up or down to nearest whole year.

Age when quit using the substance?

This element is only shown when the option "Not currently, but previously" is selected in the question "Substance (other than tobacco or alcohol) use?"

Please round up or down to nearest whole year.

Frequency of physical activity

Include physical exercise (sports, fitness, etc.) or walking activity for 1 hour or more.

- ○ Daily
- ○ Two or three times a week
- ○ Weekly
- ○ Occasionally
- ○ Never

Page break

Mandatory fields are marked with a star *

ASSESSMENT OF CHRONIC SOMATIC COMORBIDITY

Heart disease (heart only) *

- ◉ No
- ○ Yes

Is the patient's heart disease severe? *

This element is only shown when the option "Yes" is selected in the question "Heart disease (heart only)"

- ○ No
- ○ Yes
- ○ Don't know (describe)

Describe the patient's heart disease

This element is only shown when the option "Don't know (describe)" is selected in the question "Is the patient's heart disease severe?"

Hypertension (the severity of which is assessed, the organs involved are considered separately) *

- ◉ No
- ○ Yes

Is the patient's hypertension severe? *

This element is only shown when the option "Yes" is selected in the question "Hypertension (the severity of which is assessed, the organs involved are considered separately)"

- ○ No
- ○ Yes
- ○ Don't know (describe)

Describe the patient's hypertension

This element is only shown when the option "Don't know (describe)" is selected in the question "Is the patient's hypertension severe?"

Vascular pathologies (blood, vessels, marrow, spleen, lymphatic system) *

- ◉ No
- ○ Yes

Is the patient's vascular pathology severe? *

This element is only shown when the option "Yes" is selected in the question "Vascular pathologies (blood, vessels, marrow, spleen, lymphatic system)"

- ○ No
- ○ Yes
- ○ Don't know (describe)

Describe the patient's vascular pathology

This element is only shown when the option "Don't know (describe)" is selected in the question "Is the patient's vascular pathology severe?"

Respiratory diseases (lungs, bronchi, trachea under the larynx) *

- ◉ No
- ○ Yes

Is the patient's respiratory disease severe? *

This element is only shown when the option "Yes" is selected in the question "Respiratory diseases (lungs, bronchi, trachea under the larynx)"

- ○ No
- ○ Yes
- ○ Don't know (describe)

Describe the patient's respiratory disease

This element is only shown when the option "Don't know (describe)" is selected in the question "Is the patient's respiratory disease severe?"

O.O.N.G.L. (eye, ear, nose, throat, larynx) *

- ◉ No
- ○ Yes

Annex II

Ethical Committee approvals to clinical sites

Dictamen Modificación Favorable
C.P. CONNECT-AD - C.I. 18/422-E_BS
04 de noviembre de 2020

Dra. Mar García Arenillas
Presidenta del CEIm Hospital Clínico San Carlos

CERTIFICA

1º. Que el CEIm Hospital Clínico San Carlos ha evaluado la propuesta del promotor para que se realice la enmienda con número de referencia **H2020-SC1-2020-Single-Stage-RTD 964220 - AI-Mind** en el estudio:

Título: Estudio del conectoma anatomo-funcional de familiares de enfermos de Alzheimer: una propuesta de intervención temprana cognitiva y de estilo de vida (CONNECT-AD).
Código Interno: 18/422-E_BS
Investigador: Fernando Maestú Unturbe

2º. La enmienda solicita:

Estudio de extensión titulado **"Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment (AI-Mind)"**

3º. Este CEIm en su reunión del día 04/11/2020, acta 11.1/20 emite un **DICTAMEN FAVORABLE** para la realización de la modificación al estudio en el centro.

Lo que firmo en Madrid, a 04 de noviembre de 2020

GARCIA ARENILLAS MARIA DEL MAR - 05250249Q

Firmado digitalmente por GARCIA ARENILLAS MARIA DEL MAR - 05250249Q
Fecha: 2020.11.05 07:53:30 +01'00'

Fdo.: Dra. Mar García Arenillas
Presidenta del CEIm Hospital Clínico San Carlos

Kokoustiedot

Aika 22.09.2021 keskiviikko klo 13:30 - 15:55

Paikka Teams etäkokous

Lisätietoja Eettisen toimikunnan IV kokous 15/2021

Osallistujat

Läsnä	Markus Perola, puheenjohtaja Sirpa Soini, varapuheenjohtaja Jouni Lauronen, varapuheenjohtaja Virve Koljonen Simo Kyllönen Kristiina Junttila Kirsi Lindfors Merja Rukko, maallikko Jukka Kilpeläinen, maallikko Marjaana Tiainen Tapio Vehmas
Muut osallistujat	Piia Paavilainen, toimikuntasihteeri Karin Blomgren, tutkimusylilääkäri, § 146
Poissa	Vesa Kontinen

§ 147 Asianro HUS/2523/2021

Tutkimuksen nimi **AI Mind: toiminnalliseen aivokuvantamiseen perustuvia välineitä dementian diagnostiikkaan. AI Mind: intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment; Uusi tutkimussuunnitelma**

Salassapitoperuste Llt488/1999 §23; Eettisen toimikunnan lausuntoasia

Esittelijä Tapio Vehmas, dosentti, ylilääkäri

Kuvaus Toimikunnan käsiteltäväksi on toimitettu uusi tutkimussuunnitelma.

Kyseessä on tutkimus, jonka tavoitteena on kehittää tekoälyyn ja toiminnalliseen aivokuvantamiseen perustuvia kliinisiä työvälineitä dementian ennustamiseen neljässä kliinisessä keskuksessa (Helsinki, Oslo, Madrid, Rooma). Synaptisten toimintahäiriöiden seurauksena syntyvät aivoverkostojen muutokset tiedetään varhaiseksi riskitekijäksi, jota pyritään kartoittamaan tässä tutkimuksessa elektroenkefelografian (EEG) ja magnetoenkefalografian (MEG) avulla. Tutkimuksen tavoitteena on parantaa kykyämme ennustaa MCI-potilaiden dementiariskiä pystyäksemme löytämään aiempaa suuremmalla tarkkuudella ne potilaat, jotka hyötyvät kliinisestä interventiosta, ja siten viivästyttämään dementian kehittymistä.

Toimikunnalle ilmoitettu tutkimuksen aikataulu
1.12.2021–7.9.2026

Tutkimuksesta vastaava henkilö
Hanna Renvall, dosentti, HUS

Tutkimusryhmä
Hanna Renvall, dosentti
Mia Liljeström
Ville Mäntynen
Antti Kinnunen, lisensiaatti
Jari Kainulainen, AMK
Päivi Olli, AMK
Anne Koivisto
Susanna Melkas, professori
Marja Hietanen, dosentti
Teemu Paalanen, maisteri
Perttu Laamanen

Toimeksiantaja Tutkijalähtöinen tutkimus

Tutkimuksen rahoitus EU Horizon2020

Toimitetut asiakirjat

0 Eettinen lausuntohakemus.pdf
Liite1 Rekisteriseloste ja vaikutustenarviointi AIMind 080921.pdf
Liite2 Kustannusarvio ja rahoitussuunnitelma 080921.pdf
Liite3 Arvio eettisyydesta AIMind 080921.pdf
Liite4 Suostumuslomake AIMind 080921.pdf
Liite5 Research plan AIMin 080921.pdf
Liite6 Tutkimussuunnitelman lyhennelmä AIMind 080921.pdf
Liite7 CV 080921.pdf
Liite8 DTA AIMind 080921.pdf
Liite9 Sisaanottokriteerit AIMind 080921.pdf
Liite10 HUS Budget 080921.pdf
Liite11 Tutkimusryhmä.pdf

Päätösesitys

Eettinen toimikunta päättää

1. asiasta kokouskäsittelyssä,

2. periä lausuntomaksuna 0 € (STM:n asetus 1171/2020, 1 § 3 mom.).

Päätös

Toimikunta katsoo, että tutkimussuunnitelma ja sen liiteasiakirjat noudattavat lääketieteellisestä tutkimuksesta annetun lain (488/1999 myöh. muutoksineen) ja asetuksen (986/1999 myöh. muutoksineen), lain terveydenhuollon laitteista ja tarvikkeista (629/2021), lain ihmisen elimien, kudoksien ja solujen lääketieteellisestä käytöstä (101/2001), biopankkilain (688/2021), lain sosiaali- ja terveystietojen toissijaisesta käytöstä (552/2019, § 55) sekä lain potilaan asemasta ja oikeuksista (785/1992) säännöksiä.

Tutkimuksen rekisterinpitäjä vastaa tutkimuksessa käytettävien henkilötietojen käsittelystä kaikissa tilanteissa.

Eettinen toimikunta pitää tutkimussuunnitelmaa eettisesti hyväksyttävänä ja päättää

1. antaa siitä puoltavan lausunnon. Toimikunta kuitenkin edellyttää, että asiakirjoihin tehdään seuraavat korjaukset:
- Tutkimussuunnitelmana on toimitettu EU-hakemus ja on siksi hyvin yksityiskohtainen ja rönsyilevä sisältäen mm. erilaisia kaavakepohjia runsaasti, tutkimussuunnitelman lyhennelmä taas melko niukka. Eettinen toimikunta kaipaa tarkempaa kuvausta siitä, miten suomalaista tutkittavaa koskeva ison konsortion suomalainen osa suoritetaan ja miten se eroaa, vai eroaako, EU-hakemuksen kokonaisuudesta. Tämän voi toimittaa esimerkiksi nyt liitteenä olleen lyhennelmän laajennuksena.
- Henkilötietoja sanotaan kerättävän tutkittavalta, HUSLABista, Kannasta ja Apotista. Yhdistelyyn tarvittavat luvat ja data hankittaneen Findatasta toisiolain perusteella? Tämä pyydetään lisäämään asiakirjoihin.
- Täsmentämään suostumuslomakkeessa kohtaa "Kaikki sinua koskevat tiedot anonymisoidaan viiden vuoden kuluttua siitä

hetkestä, jolloin aineistoa on viimeksi käytetty tieteelliseen tarkoitukseen."
- Korjaamaan suostumuslomakkeessa kohtaa " Jos peruutan suostumukseni, minusta peruuttamiseen mennessä kerättyjä tietoja ja/tai näytteitä ei enää käytetä tutkimustarkoituksessa, vaan ne hävitetään." Menetelmätutkimuksessa tietoja pitää voida käyttää, kuten asetuksessa on mainittu.
- Tutkimus kestää 2 vuotta ja siitä ei ole tutkittaville suoranaista hyötyä. Olisi kohtuullista maksaa tutkittaville asetuksessa säädetty haittakorvaus.

Päätöstä koskeviin asiasisällöllisiin kysymyksiin vastaa tarvittaessa esittelijä / puheenjohtaja.

2. periä lausuntomaksun esityksen mukaisesti.

Puoltava lausunto astuu voimaan, kun puheenjohtaja on sähköisesti hyväksynyt pyydetyt korjaukset/lisäselvitykset, ja asiasta on lähetetty lausunto.

Korjausten/selvitysten toimittaminen

Toimikunnan esittämiin korjauspyyntöihin tulee vastata kohta kohdalta. Tehtyjen muutosten tulee näkyä selkeästi muutetuissa asiakirjoissa. Lisäykset tekstiin tehdään tekstin korostusvärillä ja tekstin poistot yliviivaten. Mikäli tekstiin tehdään muutoksia sivujen marginaaliin esimerkiksi tekstinkäsittelyohjelman "näytä korjaukset" ("track changes") -toiminnon perusasetuksia käyttäen, tulee asiakirja muuttaa pdf-muotoon ennen sen liittämistä Tutkijan työpöydälle.

Liitteenä on toimitettava kopio pöytäkirjanotteesta, johon tehty korjaus/selvitys perustuu. Toimikunta haluaa myös erillisen vastineen toimikunnan antamiin korjauspyyntöihin, toisin sanoen kirjallisen selvityksen siitä, mitä korjauksia asiakirjoihin on tehty.

Näitä korjauksia ei tarvitse toimittaa enää toimikuntaan käsiteltäväksi vaan ainoastaan Tutkijan työpöydällä alkuperäisen eettisen lausuntohakemuksen kautta puheenjohtajan hyväksyttäväksi (Ohjattu prosessi: Eettinen lausuntohakemus – Lisäselvitykset ja korjaukset puheenjohtajalle).

Eettisen toimikunnan antamasta lausunnosta ei voi valittaa. Jos eettisen toimikunnan lausunto on kielteinen, toimeksiantaja voi saattaa asian saman sisältöisenä uudelleen eettisen toimikunnan käsiteltäväksi. Alueellisen eettisen toimikunnan on toimeksiantajan pyynnöstä hankittava asiasta ennen uuden lausuntonsa antamista valtakunnallisen lääketieteellisen tutkimuseettisen toimikunnan lausunto (Tutkimuslaki 488/1999 myöh. muutoksineen).

Maksuvelvollinen, joka katsoo, että maksun määräämisessä on tapahtunut virhe, voi vaatia oikaisua. Oikaisuvaatimusohje on liitteenä.

Lisätietoja

Esittelijä Tapio Vehmas, tapio.vehmas@ttl.fi
Puheenjohtaja Markus Perola, markus.perola@thl.fi
Toimikuntasihteeri Piia Paavilainen, p. 050 427 9493, piia.paavilainen@hus.fi

Jakelu

HUS Kuvantaminen, kliininen neurofysiologia, Hanna Renvall

Otteen tarkastamattomasta pöytäkirjasta oikeaksi todistaa
Helsingissä 27.9.2021

Piia Paavilainen
sihteeri

Lähetetty tiedoksi 27.9.2021

Liite Oikaisuvaatimusohje

Oikaisuvaatimus lausuntomaksua koskevaan päätökseen

Oikaisuvaatimusoikeus

Eettisen toimikunnan tutkimussuunnitelmasta tai sen muutoksesta määräämään lausuntomaksuun voidaan hakea oikaisua. Oikaisuvaatimuksen saa tehdä se, johon päätös on kohdistettu tai jonka oikeuteen, velvollisuuteen tai etuun päätös välittömästi vaikuttaa (asianosainen). Kuntayhtymän viranomaisen päätöksestä saa tehdä oikaisuvaatimuksen myös kuntayhtymän jäsenkunta ja sen jäsen.
Oikaisuvaatimus tehdään kirjallisena.

Oikaisuvaatimuskielto

Oikaisuvaatimusta ei saa tehdä päätöksestä, joka koskee vain valmistelua tai täytäntöönpanoa, oikaisuvaatimuksen johdosta annetusta päätöksestä eikä päätöksestä, johon haetaan muutosta muun lain kuin kuntalain (410/2015) nojalla.
Tutkijalla tai muulla asianosaisella taikka kuntayhtymän jäsenkunnalla tai sen jäsenellä ei ole oikeutta vaatia oikaisua eettisen toimikunnan antamaan lausuntoon. Mikäli eettisen toimikunnan lausunto on kielteinen, toimeksiantaja voi saattaa asian uudelleen eettisen toimikunnan käsiteltäväksi. Alueellisen eettisen toimikunnan on toimeksiantajan pyynnöstä hankittava asiasta ennen uuden lausuntonsa antamista valtakunnallisen lääketieteellisen tutkimuseettisen toimikunnan lausunto.

Oikaisuvaatimusviranomainen

Eettisen toimikunnan tekemästä lausuntomaksua koskevasta päätöksestä oikaisuvaatimus tehdään HUSin hallitukselle.

Oikaisuvaatimusaika

Oikaisuvaatimus on tehtävä 14 päivän kuluessa päätöksen tiedoksisaannista. Asianosaisen katsotaan saaneen päätöksestä tiedon, jollei muuta näytetä, seitsemän päivän kuluttua kirjeen lähettämisestä, kolmantena päivänä sähköisen viestin lähettämisestä, saantitodistuksen osoittamana aikana tai erilliseen tiedoksisaantitodistukseen merkittynä aikana. Kunnan jäsenen katsotaan saaneen päätöksestä tiedon seitsemän päivän kuluttua siitä, kun pöytäkirja on nähtävänä yleisessä tietoverkossa.
Tiedoksisaantipäivää ei lueta oikaisuvaatimusaikaan. Jos oikaisuvaatimusajan viimeinen päivä on pyhäpäivä, itsenäisyyspäivä, vapunpäivä, joulu- tai juhannusaatto taikka arkilauantai, saa oikaisuvaatimuksen toimittaa perille ensimmäisenä arkipäivänä sen jälkeen.

Oikaisuvaatimuksen sisältö

Oikaisuvaatimuksessa on ilmoitettava:

- päätös, johon vaaditaan oikaisua,
- miltä kohdin päätökseen vaaditaan oikaisua ja mitä muutoksia siihen vaaditaan tehtäväksi,
- oikaisuvaatimuksen perustelut,
- mihin oikaisuvaatimusoikeus perustuu, ellei oikaisuvaatimuksen kohteena oleva päätös kohdistu sen tekijään,
- oikaisuvaatimuksen tekijän nimi, kotikunta ja yhteystiedot,

- mahdollisen asiamiehen tai laillisen edustajan yhteystiedot sekä
- postiosoite ja mahdollinen muu osoite, johon asiaan liittyvät asiakirjat voidaan lähettää.

Oikaisuvaatimuksen liitteet

Oikaisuvaatimukseen on liitettävä:

- oikaisuvaatimuksen kohteena oleva päätös oikaisuvaatimusohjeineen,
- selvitys siitä, milloin oikaisuvaatimuksen tekijä on saanut päätöksen tiedoksi, tai muu selvitys oikaisuvaatimusajan alkamisajankohdasta sekä
- asiakirjat, joihin oikaisuvaatimuksen tekijä vetoaa vaatimuksensa tueksi, ellei niitä ole jo aikaisemmin toimitettu viranomaiselle.

Tiedon luovuttamiseen salassa pidettävistä asiakirjoista sovelletaan viranomaisten toiminnan julkisuudesta annetun lain (621/1999) säännöksiä.

Oikaisuvaatimuksen perille toimittaminen

Asianosaisen tai hänen valtuuttamansa henkilön on toimitettava HUSin hallitukselle osoitettu oikaisuvaatimus HUS Keskuskirjaamoon.
HUS Keskuskirjaamo
Osoite: PL 200, 00029 HUS
Käyntiosoite: Marjaniementie 74, Iiris-keskus, 00930 Helsinki
Puh. vaihde: 09 4711
Puh. 050 428 7837
Faksi: 09 471 75500
keskuskirjaamo@hus.fi
Asiakaspalveluaika arkisin klo 9.00–15.00
Oikaisuvaatimus on jätettävä niin ajoissa, että se ehtii perille oikaisuvaatimusajan viimeisenä päivänä ennen HUS Keskuskirjaamon asiakaspalveluajan päättymistä. Omalla vastuulla oikaisuvaatimuksen voi lähettää postitse, lähetin välityksellä tai faksilla taikka sähköpostilla.

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Prot. ID 4370

Chiar.mo Prof. Camillo MARRA
Direttore UOSD CLINICA MEMORIA

Egr. Avv. Filippo E. LEONE
Responsabile Grant Office

S E D E

Egr. Dott. Ira HARALDSEN
Ospedale Universitario di Oslo

Oggetto: PROT. H-2020-SC1-BHC-06-2020 **'AI MIND Strumenti di intelligenza digitale per lo screening di connettività cerebrale e stima del rischio di demenza in soggetti affetti da Disturbo Cognitivo Minimo (MCI)" [Grant Agreement n 964220]'**

Chiarissimo Professore,

si comunica che il Comitato Etico (CE) ha preso atto ed approvato la nuova versione del consenso informato (versione 3 del 31/08/2021), la lettera di risposta da parte del PI (datata 31/08/2021) e la modulistica centro-specifica aggiornata. Tali documenti sono stati depositati con email dello 01/09/2021 e dello 06/09/2021 in risposta a quanto prescritto da questo CE nella seduta del 22/07/2021.
Si fa presente che lo studio potrà avere inizio a seguito del rilascio della delibera amministrativa.
Cordiali saluti

Il Presidente del Comitato Etico

Prof. Andrea Bacigalupo

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst D	Finn Skre Fjordholm	+47 22 84 58 21	13.04.2021	204084
			Deres referanse:	

Ira Haraldsen

204084 AI-MIND-prospektiv studie

Forskningsansvarlig: Oslo universitetssykehus HF

Søker: Ira Haraldsen

REKs vurdering

Vi viser til søknad om prosjektendring datert 30.03.2021 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst D på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringen gjelder:

-Nytt informasjonsskriv (31.03.2021).

-Rutine for tilbakemelding til deltagerne

Det er foretatt endringer i tråd med komiteens vedtak den 03.03.2021.

Det legges nå opp til at deltagerne må reservere seg mot at resultater overføres til fastlegen.

Komiteens leder har vurdert de omsøkte endringene, og har ingen forskningsetiske innvendinger til endringene slik de er beskrevet i skjema for prosjektendring.

Vedtak

Godkjent

REK har gjort en forskningsetisk vurdering av endringen i prosjektet, og godkjenner prosjektet slik det nå foreligger, jf. helseforskningsloven § 11.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Med vennlig hilsen,

Finn Wisløff
Professor em. dr. med.
Leder

Finn Skre Fjordholm
rådgiver
REK sør-øst D

Kopi til: Oslo universitetssykehus HF

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

IRCCS San Raffaele
Roma

Presidio Ospedaliero: via della Pisana, 235 | 00163 Roma | Centralino: 06 6660 [illegible]affaele.it
Research Centre: via di Val Cannuta, 247 | 00166 Roma | Tel. 06 5225 34[illegible]
www.sanraffaele.it

Comitato Etico IRCCS San Raffaele Roma
Decreto Ministero della Salute 08 febbraio 2013
Modifica alla DGR n. 146 del 12/06/2013
Deliberazione Regione Lazio n. 301 del 03/10/2013

Roma, il 26/07/2021

Pag. 2 con la presente + allegati

Al Promotore *IRCCS San Raffaele Roma*

Al Richiedente e Sperimentatore Principale *Prof. P. M. Rossini*

Dipartimento di *Scienze Neurologiche e Riabilitative*

Oggetto: Comunicazione del parere relativo alla richiesta di approvazione alla conduzione dello studio clinico dal titolo: *Strumenti di intelligenza digitale per lo screening di connettività cerebrale e stima del rischio di demenza in soggetti affetti da Disturbo Cognitivo Minimo (MCI).*

Codice Protocollo: **AIMIND**
Numero Registro Pareri **21/13**

In riferimento alla richiesta di cui all'oggetto, si trasmette il parere del Comitato Etico dell'IRCCS San Raffaele Pisana riunitosi in data **21/07/2021**

In osservanza alle legislazioni vigenti in materia di sperimentazione clinica, il Comitato Etico ha esaminato la richiesta di parere relativa allo studio in oggetto.

Avendo valutato la documentazione allegata alla lettera di trasmissione datata 15/07/2021 (la cui lista è riportata nell'appendice 1 a questo verbale).

Il Comitato etico ha espresso PARERE FAVOREVOLE condizionato alle seguenti richieste:

il Comitato etico attende che il PI firmi la dichiarazione su modulo AIFA che attesta che lo studio è osservazionale.
Se, come compreso in preistruttoria, l'analisi di APOE e Tau-181 verrà eseguita - centralmente - su una aliquota di sangue che viene comunque prelevata al paziente per eseguire valutazioni nella normale pratica clinica, si chiede di precisare tale procedura in fondo alla dichiarazione di studio osservazionale confermando che non viene eseguito un prelievo *ad hoc* per questa valutazione.

Una volta ottenuto il nuovo documento, lo studio potrà iniziare appena ottenuta la delibera a procedere.

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Comitato Etico IRCCS San Raffaele Roma
Decreto Ministero della Salute 08 febbraio 2013
Modifica alla DGR n. 146 del 12/06/2013
Deliberazione Regione Lazio n. 301 del 03/10/2013

Elenco dei componenti del CE votanti, presenti alla discussione tenutasi in modalità telematica e che hanno dichiarato assenza di conflitti di interessi di tipo diretto o indiretto:

1. Dott. Nicola Barbato, Rappresentante professioni sanitarie infermieristiche, tecniche e della riabilitazione
2. Prof. Vincenzo Barbieri, Esperto in materia giuridica e assicurativa
3. Prof. Lucio Capurso, Clinico, presiede la riunione
4. Dott. Claudia Condoluci, Pediatra
5. Dott. Salvatore D'Antonio, Rappresentante del volontariato per l'assistenza e associazionismo di tutela dei pazienti
6. Dott. Angela Frazzetto, Farmacista IRCCS San Raffaele Roma (componente ex officio)
7. Mons. Andrea Manto, Esperto di Bioetica
8. Dott. Daniela Pernice, Esperto di Bioetica
9. Dott. Stefania Proietti, Biostatistico
10. Prof. Fabrizio Stocchi, Clinico nell'ambito della Neurologia
11. Prof. Carlo Tomino, Farmacologo

A chiamata
Ing. Fabrizio Vecchio, Ingegnere Clinico

Si ricorda che è obbligo notificare al Comitato Etico: data di **arruolamento** del primo paziente e data di **conclusione** dello studio a livello locale ed a livello globale; stato di **avanzamento** dello studio con cadenza annuale; fine del periodo di arruolamento; **risultati dello studio**, entro un anno dalla conclusione della stessa.

Il Proponente deve ottemperare alle disposizioni legislative vigenti e riferire immediatamente al Comitato relativamente a: **deviazioni dal protocollo**, anche quando queste si rendano necessarie per eliminare i rischi immediati per i partecipanti; modifiche al protocollo, che non potranno essere messe in atto senza che il Comitato abbia rilasciato parere favorevole ad uno specifico emendamento, eccetto quando ciò sia necessario per eliminare i rischi immediati per i partecipanti o quando le modifiche riguardino esclusivamente aspetti logistici o amministrativi dello studio; **informazioni** relative ad eventi e condizioni potenzialmente **in grado di incidere negativamente sul rapporto tra rischi e benefici attesi** per i partecipanti (ad es. reazioni avverse serie) e/o che incidano significativamente sulla conduzione dello studio (tutte le reazioni avverse serie).

Il Presidente

Lucio Capurso

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Research Centre: via di Val Cannuta, 247 | 00166 Roma | Tel. 06 5225 3406
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Allegato 1 Elenco della documentazione esaminata

Tipo documento	Versione e data	Nome File
Elenco Centri Partecipanti	n. 01 – 10/07/2021	AIMind_ElencoCentriPartecipanti
Dichiarazione di Fattibilità	n. 01 – 10/07/2021	AIMind_Fattibilità
Consenso Informato	n. 01 – 10/07/2021	AIMind_ConsensoInformatoENG
		AIMind_ConsensoInformatoITA
Consenso Trattamento dei Dati	n. 01 – 10/07/2021	AIMind_ConsensoTrattamentoDati
Lettera al Medico Curante	n. 01 – 10/07/2021	AIMind_LetteraalMedicoCurante
Parere del CE centro coordinatore	n. 01 – 10/07/2021	AIMind_CECentroCoordinatore
Protocollo di Studio	n. 01 –10/07/2021	AImind_Protocollo
Sinossi	n. 01 – 10/07/2021	AIMind_SinossiITA
		AIMind_SinossiENG
Conflitto di interessi	n. 01 – 10/07/2021	AIMind_ConflittoInteressi
Dichiarazione di nessuna indennità per mancato guadagno o rimborso spese	n. 01 – 10/07/2021	AIMind_DichiarazioneIndennità
Budget Plan dello studio	n. 01 – 10/07/2021	AIMind_Budget
Richiesta esonero Oneri	n. 01 – 10/07/2021	AIMind_EsoneroOneriCE
Invitation to Italy		AIMind_InvitationtoItaly
Variabili Cliniche	n. 01 – 10/07/2021	AIMind_ClinicalVariables
Grant Agreement	n. 01 – 17/03/2021	AI-Mind_CA_Version 1_Fully signed