Evaluation of a Computerized Complex Instrumental Activities of Daily Living Marker (NMI) (AltoidaML)

RESEARCH PROTOCOL

Version 2.0, April 6th 2016

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Protocol ID	altoidaML01
Short title	Evaluation of a Computerized Complex Instrumental Activities of Daily Living Marker (NMI) (AltoidaML)
Version	2.0
Date	April 6th, 2016
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Subsidizing party	RADAR-AD receives funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 806999. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. See www.imi.europa.eu for more details.
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Principal Investigator: Add local P.I.		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

1MWT	**One-minute walking test**
AD	**Alzheimer's disease**
ADL	**Activities of Daily Living**
AE	**Adverse Event**
APOE	**Apolipoprotein E**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects**
CDR	**Clinical Dementia Rating**
CSF	**Cerebrospinal Fluid**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
DSST	**Digit Symbol Substitution Test**
EADC	**European Alzheimer's Disease Consortium**
ECog	**Everyday Cognition**
ESS	**Epworth Sleepiness Scale**
GPS	**Global Positioning System**
iADL	**Instrumental Activities of Daily Living**
IMI	**Innovative Medicines Initiative**
LAR	**Legal Authorized Representative**
MEA	**Momentarily Ecological Assessment**
METC	**Medical research ethics committee (MREC)**
MMSE	**Mini-Mental State Examination**
MRI	**Magnetic Resonance Imaging**
NPI-Q	**Neuropsychiatric Inventory Questionnaire**
PAB	**Patient Advisory Board**
PSQI	**Pittsburgh Sleep Quality Inventory**
RADAR-AD	**Remote Assessment of Disease and Relapse – Alzheimer's Disease**

RADAR-CNS	**Remote Assessment of Disease and Relapse – Central Nervous System**
RMT	**Remote Measurement Technologies**
(S)AE	**(Serious) Adverse Event**
SFS	**Social Functioning Scale**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VSWM	**Visuo-Spatial Working Memory**
WMO	**Medical Research Involving Human Subjects Act**

SUMMARY

Alzheimer's disease (AD) is associated with staggering costs and suffering, which are particularly related to the social impacts of caring for increasingly disabled individuals. These functional disabilities can be almost undetectable in the early stages of the disease, worsening over time often and at a varying rate of progression in different people. The measurement of such functional disabilities is typically blunt and relies on direct observation or caregiver recall. Digital technologies, particularly those based on the use of smartphones, wearables and/or home-based monitoring devices, here defined as 'Remote Measurement Technologies' (RMTs), provide an opportunity to change radically the way in which functional assessment is undertaken in AD, RMTs have the potential to obtain better measurements of behavioural and biological parameters associated with individual Activities of Daily Living (ADL) when compared to the current subjective scales or questionnaires. Divergence from normative ADL profiles could objectively indicate the presence of specific incipient functional impairments even at the very early stages of AD. Therefore, the main hypothesis of this project is that RMTs should allow the detection of impairments in functional component of ADLs that occur below the threshold of clinical scale detection or disability questionnaires.

Objectives: The primary objective of this study is to assess the performance of selected RMTs against standardised rating scales of ADLs in subjects with preclinical AD dementia, MCI due to AD dementia, and mild-to-moderate AD dementia. Secondary objectives are, (a) to evaluate associations between RMTs and standard clinical scales used to characterise people with AD diagnosis, (b) to investigate the patient acceptability of selected RMTs used for the duration of the study, and (c) to assess the technical performance of RMTs and digital platform in a real-life setting.

Study design: A multicentre observational cross-sectional cohort digital assessment study lasting 5 years, with a sub-study extension of at-home monitoring for 4 weeks.

Study population: Subjects (n=283) with positive AD biomarkers, e.g positive brain Abeta (Aβ) deposition confirmed by amyloid PET or CSF Aβ test at the preclinical AD, MCI due to AD, and mild-to-moderate AD dementia stages, and age-and gender matched control subjects (n=213) aged over 50 years with a caregiver/family member available to contribute to the study.

Primary outcome measure: statistically significant difference between healthy volunteers, preclinical AD, MCI due to AD, and mild-to-moderate AD dementia in outcome measures of ADL using selected RMTs.

1. **Secondary Outcome measurements:** Statistically significant difference between healthy volunteers, preclinical AD, MCI due to AD, and mild-to-moderate AD dementia using RMTs, neuropsychological assessment like CDR and Altoida's cognitive scale. Finally the relationship of genes or biomarkers with risk of RMT progression, and longitudinal correlation changes in biomarkers with rate of RMT progression.

2. Assess effectiveness of disease modifying therapy such as aducanumab in real world clinical practice on subjects who will initiate disease modifying therapy for AD treatment during the study by using neuropsychological assessment such as CDR and fluid biomarker including blood and CSF and so on.
3. Assess effectiveness of disease modifying therapy such as aducanumab in real world clinical practice on subjects who will initiate disease modifying therapy for AD treatment during the study by using RMTs and Altoida's cognitive scale.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Subjects will visit the clinic at least thirteen times: once for a baseline visit and once at the end of the study. During these visits, information gathering, clinical profiling, neurophysiological testing and training in the use of RMTs will be performed. Up to fourteen telephone interviews will be held during the study duration of 5 years to assess user experience, technical problems with the RMTs and adverse events. The study will not have any direct benefits for participants.

1. INTRODUCTION AND RATIONALE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a cascade of pathological events, including abnormal extracellular deposition of amyloid-beta (Aβ) plaques, intracellular tau tangles, and volumetric loss of cortical gray matter (Jack et al. 2018). Clinically, AD is characterized by several syndromic stages defined by a combination positive biomarker signals (e.g., Aβ load in CSF or brain tissue), various levels of cognitive impairment and different stages of dementia. Current consensus is that AD pathophysiology is already present in the brain long before the onset of clinical symptoms. This so-called 'preclinical' disease phase can last for up to 20 years, being characterised primarily by biomarker positivity despite normal cognitive performance. The first clinical symptom generally observed in AD patients is short-term memory deficits, sometimes associated with modest impairments in other cognitive domains. This syndromic phase is referred to as 'prodromal AD' or Mild Cognitive Impairment (MCI) stage. As the disease progresses, AD patients experience a progressive loss of cognitive capacities in multiple domains, which significantly interfere with activities of daily living (ADL). This final syndromic phase is referred to as the 'dementia' stage of AD typically subdivided in mild, moderate AD and severe AD dementia, based on the severity of cognitive impairment and the levels of functional decline.

Especially when patients reach the dementia stage of AD, the disorder is associated with staggering costs to the health care system, health insurance and families. These costs relate particularly to the social-and economic impacts of caring for individuals with increasing functional disabilities. These functional disabilities start as almost undetectable in the preclinical disease phase, worsening over time, often at varying rates in different people at the MCI due to AD stages. A very early detection of the presence of functional decline in preclinical AD may eventually help in adopting a different lifestyle or motivate the acceptance of effective therapeutic intervention, at least those presently available. However, current standard measurements of functional disabilities based on scales or questionnaires are typically blunt and insensitive to change. The main reason is that the scores are based on either individual self-appreciation, caregiver recall or physician-rated direct observations (subjective). Scoring these scales or filling questionnaires based on predefined syndromic constructs that require judgement about the "average" performance occurring in periods spanning through either weeks or months (integration over large time-span), hence only very modestly accurate. In addition, measurement of disabilities is typically performed once every several months (low frequency) and during hospital visits (clinical setting). RMT digital technologies such as smartphones, wearable devices, e.g. actigraphy and home-based monitoring devices can provide an opportunity to change radically the way in which functional assessment is undertaken in AD. The build in sensors are non-invasive, ie patients are not

aware of measurements being taken and allow detailed measurements of parameters associated to symptoms or specific behaviour (objective) and of activities of direct relevance for quality of life (ecological), measured when the behaviour occurs (momentarily, high frequency), either measured continuously or once/twice day over months (high frequency), generally performed at home or outdoor (non-clinical setting, real life) without the need to frequently visit a hospital. Ultimately, such technologies may allow us to move from a "diagnose and treat" to a "predict and preempt" model of care [1]. This approach will become of value when reliable therapeutics aimed to slow down the progression of the disease will be available hopefully allowing patients in the earliest stages of AD to live independently for longer. Unfortunately, despite considerable progress in our understanding of the neuropathology of AD, this progress has not been translated into novel drug treatments, partially due to the low assay sensitivity of the clinical measurements included so far in the clinical studies. Therefore, RMT may provide a possible solution to this problem.

The current study is part of the Innovative Medicine Initiative (IMI) funded Remote Assessment of Disease And Relapse (RADAR) consortium. The goal of RADAR-AD is the development and initial validation of technology-enabled, quantitative and sensitive measures of functional decline by assessing Activities of Daily Living (ADL) in patients in various stages of the AD progression. The RADAR-AD team has identified and singled out from the literature a series of functional disabilities that potentially affect the subject's daily life in early phases of the AD. Relevant outcome measures for the study have been selected through the following longitudinal process:

1. Identification of functional domains that meet one or more of the following criteria:
    - Predicts conversion of MCI due to AD to mild AD dementia.
    - Impaired in mild AD dementia.
    - Predicts functional decline in AD dementia.
    - Reported as important by an AD dementia patient advisory board.
2. Identification of candidate RMT to cover real-life measurement of the functional domains identified in step 1.
3. Identification of candidate digital biomarkers to cover clinical measurement of the functional domains identified in step 1.

Functional domains, RMTs, and clinical assessments that resulted from the selection process above are listed in Tables 1, and 2. The selection process described in step 1 resulted in the identification of the following functional domains, sorted by relevance (HR=highly relevant, R=relevant, N=neutral, LR=least relevant). See appendix A for a reference list regarding the functional domain selection process.

Table 1: selected functional domains and their relevance

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Functional domain	Relevance	Predicts MCI->AD dementia conversion	Impaired in early AD	Predictive of decline	Reported by PAB
1. Difficulties at work	HR	x	X	x	x
2. Spatial navigation & memory	HR	x	X	x	x
3. Planning skills & memory required for task-completion	HR	x	X	x	x
4. Managing finances	R	x		x	x
5. Self-care	R		X	x	x
6. Self-management, e.g., running errands & shopping	R	x		x	x
7. Acquiring new skills	R		X	x	x
8. Sleep quality & circadian rhythms	R		X	x	x
9. Use of technology/devices	R		X	x	x
10. Dysnomia, word finding difficulties	N		X	x	
11. Gait	N		X	x	
12. Difficulties driving	N		X	x	
13. Interpersonal interaction	N		X		x
14. Motivation, signs of apathy or withdrawal	LR				X

The central assumption of the study is that functional disabilities proportionally increase with the progressive worsening of the disorder. A recent classification proposed by the FDA 2018 guidelines for the development of novel treatments in Preclinical AD identifies the early disease progression in 3 stages: (a) Patients with characteristic pathophysiologic changes of Preclinical AD but no evidence of clinical impact (Stage 1) (b) Patients with characteristic pathophysiologic changes of AD and subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, but no functional impairment (Stage 2), and (c) Patients with characteristic pathophysiologic changes of AD and subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, but mild and detectable functional impairment. (Stage 3). The aim of the RADAR-AD study is to assess the feasibility, utility and performance of selected RMTs in profiling ADL in real-world settings [2, 3]. This goal will be achieved by evaluating digital signals collected either continuously, or daily, or weekly at home, either using wearable devices or home-located ambient devices, determining as much as possible the specific context-dependent conditions in which the signals are measured. As a general hypothesis, we expect that RMTs will deliver more sensitive and less variable measurements when compared to standard clinical assessments, questionnaires and tests measuring specific functional capabilities in the clinics.

The most important results of the present study will be (1) the evidence that some RMT parameters will provide insights for lower variance than the standard scales or

questionnaires, (2) the capacity of Altoida's NMI[1] and/or RMT to significantly differentiate the preclinical AD stages 1 & 2 when compared to healthy control, and (3) similar capabilities of Altoida's NMI and/or RMT to detect monotonic change in the MCI due to AD group and, even more, in mild-to-moderate AD dementia groups, proportional to the specific functional impairment know to worsen during the disease progression. A similar outcome to point 3 above, was obtained using the computerised Amsterdam-iADL scales [4, 5], showing a significant change in the group of individuals with subjective cognitive decline over time, resembling cognitive trajectories of the preclinical AD group of the RADAR-AD study.

2. OBJECTIVES & OUTCOMES

1. Objectives

The main objective is to assess the performance of selected RMTs against ADL standard clinical questionnaires in finding differences among individuals of various classes of severity of AD and investigate if RMT measurements are more precise and better reflect disease progression and functional /QoL changes compared to ADL standard measurements.

Secondary objectives:

- to assess associations between RMT measurements and standard clinical scales used to assess specific clinical conditions and functional impairments in AD patients;
- to assess if RMT measurements are more precise and more ecological;
- to investigate the patient acceptability and user-friendliness of selected RMTs;
- to assess the technical performance of RMTs in a real-life setting.
- to assess associations between RMT measurements, standard clinical scales and AD-related biomarker in blood and CSF
- to explore new AD-related biomarkers.

To achieve the non-invasive aspect of these objectives, measurements will be performed in clinic (i.e. under supervision of a clinical team) and in non-clinical, real life settings (i.e. at home, at work, etc.).

Primary Outcome

- Difference between healthy controls, subjects with preclinical AD, subjects with MCI due to AD, and subjects with mild-to-moderate AD dementia using selected RMTs measurements aimed to profile ADL, using diagnostic criteria as defined under 3.1.3" Both primary and secondary outcomes.

[1] Buegler, M, Harms, RL, Balasa, M, et al. Digital biomarker−based individualized prognosis for people at risk of dementia. Alzheimer's Dement. 2020; 12:e12073. https://doi.org/10.1002/dad2.12073

Secondary Outcomes

- Established clinical measures: difference between healthy volunteers, subjects with preclinical AD, subjects with MCI due to AD, and subjects with mild-to-moderate AD dementia in the following assessments of specific functions when performed in the clinic (in brackets, it is indicated which functional domain and/or main outcome measure is covered by the assessment):
    - Amsterdam-iADL
        - (orientation, planning skills & memory required for task completion household management).
    - ADCS-ADL
        - (orientation, planning skills & memory required for task completion household management).
    - CERAD neuropsychological test battery
        - (orientation, planning skills, memory required for task completion, word-finding difficulties).
    - Geriatric Depression Scale
        - (low mood, anhedonia, withdrawal).
    - Neuro Psychiatric Inventory
        - (agitation, psychoses, apathy)
        - Body Mass Index (BMI)
        - Presence diabetes or pre-diabetes diagnosis
        - Exercise, [measured with Godin Leisure-time exercise questionnaire]
        - metabolic profile (plasma cholesterol, glycaemia, HbA1S). Only if information is available a priori.
        - APOE-e4 allele genotype as obligatory measurement.
        - smoking [asked at the clinic and reported as number of cigarettes per day]
        - drinking habits [asked at the clinic and reported as units of alcohol/ week]
        - diet supplement [asked at the clinic and reported as the number of supplements currently taken]
        - hobbies [asked at the clinic using validated tools for measuring cognitive reserve and/or reported as number of activities/week (i.e., reading, crossword, puzzle solving, listening or playing music, painting, gardening, backing) the time (hour/week).

- RMT assessments: difference between healthy volunteers, subjects with preclinical AD, subjects with MCI due to AD, and subjects with mild-to-moderate AD dementia in the following assessments performed in the real world (non-clinical settings):
    - Altoida NMI telehealth version (tablet, smartphone, active interface)
        - Orientation, planning skills & spatial memory required for task completion.
        - Executive function skills & prospective memory required for task completion, short and long term.
        - Mood & anxiety
        - Voice & speech analysis
        - Accelerometer, dominant hand - arm movement,
        - Gait and motility at home etc.

- Evidence of RMT ecological value, using QoL changes, by statistical association (e.g., correlation, regression) between measurements collected in clinic vs. measurements collected in real life within the same functional domain(s).

- Quantification of passively collected sensor signals during specific ADL performance captured within context-defined, time-tagged epochs (beginning and end) repeatedly occurring over the trial period provided by:
    - the subject
    - the caregiver/informant
    - the portable camera (when available).

Table 2: list of assessments classified by test setting (clinic or real life) and completers.

Setting	Completed by	Test/device name	Frequency	Time (minutes)	Functional domain(s) and/or test domain(s) covered
Clinic	Patient	Demographics, medical history, medication use	Once	10	Life habits & AD risk factors
		Physical examination	Once	10	Life habits & AD risk factors
		Godin Leisure-time exercise questionnaire	Once	5	Life habits & AD risk factors
		CERAD test battery	Once	20	
		• Verbal fluency (animal naming)			Word finding difficulties
		• 15 item Boston Naming Test			Planning skills & memory, Word finding difficulties
		• Mini Mental State Examination			Orientation, Planning skills & memory, Word finding difficulties
		• Word list learning			Word finding difficulties
		• Word list recall			Planning skills & memory, Word finding difficulties
		• Word list recognition			Planning skills & memory, Word finding difficulties
		• Constructional praxis			Planning skills & memory
		• Delayed constructional praxis			Planning skills & memory
		Digit Symbol Substitution Test	Once	5	Planning skills & memory
		Altoida Medical Device	Once	20	Orientation, Planning skills & memory
		Physical functioning tests	Once	10	Gait
		• 1-minute walking test			
		• 1-minute dual walking test			
		• Timed up-and-go test			
		Social Functional Scale	Once	5	Maintaining social roles
		Geriatric Depression Scale	Once	5	Motivation
		Body Mass Index (BMI)	Once	5	Life habits & AD risk factors
		Clinical Dementia Rating	Once	20	Orientation, Household management, Use of technology, Maintaining social roles
		ADCS-ADL	Once	20	Orientation, Planning skills & memory, Household management
		Diabetes or pre-diabetes	Once	5	Life habits & AD risk factors
		Clinical Dementia Rating	Once	20	Orientation, Household management, Use of technology, Maintaining social roles

		Smoking	Once	5	Life habits & AD risk factors

2. Study design

The study is a multicentre, observational, cross-sectional, digital assessment cohort study in subjects with preclinical AD, MCI due to AD, and mild-to-moderate AD dementia. It consists of two parts: the main study (tier 1), where the subjects are provided with wearable digital devices, and a sub-study (tier 2), in which technologies are installed in the subjects' home (see table 2 above). The duration of the main study for individual subjects is 5 years of data collection, while for the sub-study (tier 2) a similar period of data collection is expected, with a flexible time between the two studies for arranging home-device wiring. The sub-study will be performed on those volunteers whose home setting shows the necessary technical requirements (please see table 2 above for the Residential Movement Detector).

3. STUDY POPULATION

3. Population

For the main study (tier 1), subjects with positive AD biomarkers, e.g. baseline positive brain Abeta (Ab) deposition confirmed by FDG-PET (glucose metabolic imaging) or CSF Ab test at the preclinical AD, MCI due to AD (n=283) as defined by recent EMA (2016) and FDA (2018) guidelines and by current literature [2, 3] and healthy control subjects (n=215) matched by age and gender at a group level and aged over 50 years with a caregiver/family member available to actively contribute to the study will be recruited from memory clinics and/or ongoing observational studies in 12 sites.

Subjects should be informed about the reason for eligibility for study participation before selection into the study. Patients with MCI due to AD, and mild-to-moderate AD dementia stage will be recruited from a memory clinic setting in which brain Aβ status has been disclosed as part of routine clinical care. Cognitively normal individuals (controls or preclinical AD) will be recruited from a memory clinic or research setting in which the brain Aβ status has been measured. Each site will include equal numbers of brain Aβ positive and Aβ negative cognitively normal individuals. With regards to cognitively normal individuals, disclosure of amyloid status is not required for participation in the study and will not be performed in the current study.

Some flexibility in the final total numbers for each group will be acceptable (n = +/- 5). In case subjects indicate a wish to leave the study before completion, it is up to the judgement of the local study principle investigator and the RADAR-AD team whether he/she should be replaced. This decision should be based on a combination of (1) number of days data was collected thus far, (2) compliance rate, and (3) quality of the data collected thus far. As a rule

of thumb, at least 2 years of data collection in the main study needs to be completed for a participant's data to be used in final analysis. Otherwise their data won't be used.

4. Inclusion criteria

To be eligible to participate in this study, a subject must meet the following criteria:

*For Alzheimer's disease subjects (n=*283*):*

- Male or female over 50 years of age.
- Subject is seen at a memory disorders clinic or is part of an observational study.
- A caregiver/family member or informant is available to collaborate.
- Diagnosis of individuals in the AD biological continuum with evidence of amyloid-beta accumulation based on the presence of Aβ load AD biomarkers (either in CSF or PET scan), MMSE, CDR score and cognitive tests as defined by the Guidance document of EMA (2016) or FDA (2018):
    - preclinical AD: MMSE≥27 and CDR=0, either none or borderline cognitive deficits (compatible with FDA stages 1 and 2, with positive AD biomarkers). Patients reporting subjective cognitive decline who meet the criteria above are eligible for assignment to the preclinical AD group.
    - prodromal AD/MCI due to AD: MMSE >23, CDR=0.5, impairment on cognitive testing with RBANS (compatible with stage 3 FDA, with positive AD biomarkers).
    - mild to moderate AD dementia: (MMSE>17, CDR>0.5, compatible to FDA stages 4-5.
- Informed consent signed by the subject and informant.
- In otherwise-good health condition, or with diagnosis mild chronic disorder (of metabolic, respiratory, immunological, cardiologic, and metabolic origin) or any other affections that are controlled by therapy and/or do not impair function on a secondary basis to that of AD-related symptomatology.
- Subject and caregiver should be able to read and communicate in the language of the recruitment centre and available to actively engage in tests and questionnaires.
- Subject and the caregiver/family member or informant own a smartphone.
- For those volunteering in the sub-study, their house should allow appropriate Wi-Fi and/or phone line connectivity.
- For those volunteering in the sub-study, signature on an additional Informed Consent (specifically regarding the activation – deactivation of the device during activities considered private and personal).

Healthy Control subjects (n=215):

- Male or female over 50 years of age.

- Individuals in the AD biological continuum with no evidence of amyloid-beta accumulation based on the presence of Aβ load AD biomarkers (either in CSF or PET scan).
- Approximately age and gender matched to AD subjects on a group level.
- A caregiver/family member or informant is available to collaborate.
- MMSE >27, CDR=0, no cognitive deficits at the screening visit.
- In otherwise good health conditions, or with diagnosis mild chronic disorders (of metabolic, respiratory, immunological, cardiologic, and metabolic origin) or any other affections that are controlled by the therapy and do not importantly limit ADLs or social interactions.
- Able to read and to communicate in the language of the recruitment centre.
- Informed consent signed by the subject and caregiver.
- Subject and caregiver own a smartphone.
- For those volunteering in the sub-study, their house should allow appropriate connectivity.
- For those volunteering in the sub-study, signature on an additional Informed Consent (specifically regarding the activation – deactivation of the device during activities considered private and personal).

5. Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

For Alzheimer's disease subjects:

- Presence of an additional neurological or psychiatric disease that may affect ADL, cognitive function or social interactions.
- Abnormal VB12 value.
- Any other kind of disorders that relevantly affect mobility and/or ADL, cognitive function or social interactions (e.g., immune-mediated inflammatory disorders, recovery from recent trauma, stroke confirmed by MRI, etc.).
- TSH above normal range
- T3 or T4 outside normal range with clinically significant.

Healthy Control subjects:

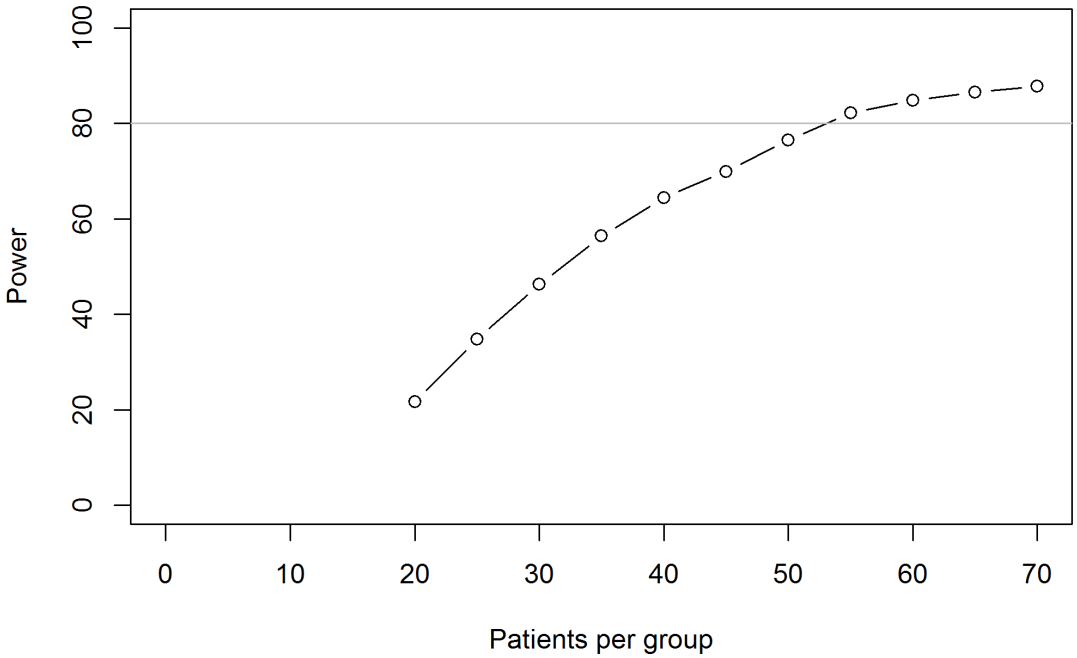
- Presence of an additional neurological or psychiatric disease that may affect ADL, cognitive function or social interactions.
- Diagnosis of any disorders or post traumatic conditions that are not fully controlled by the therapy and produce relevant limitations of ADL, cognitive function or social interactions.

6. Sample size calculation

As the primary endpoint for sample size calculation among the selected RMTs we chose the web-based version of the Amsterdam iADL questionnaire based on previous literature [4]. Sample size was chosen to have 80% power to detect a difference in functional activities of daily living of at least 10% between subjects in the following comparisons: (1) healthy controls vs. preclinical AD dementia, (2) preclinical AD vs. MCI due to AD, (3) MCI due to AD vs. mild-to-moderate AD dementia, as observed using available data from the Amsterdam's instrumental Activities of Daily Living (Amsterdam IADL) rating scale. Using the interquartile ranges presented in figure 4 of Jutten et al (2017) [4], one thousand clinical trials were simulated for each sample size considered. A trial was considered positive if all three of the abovementioned comparisons had Holm adjusted p-values < 0.05. Each comparison was performed using a two-sided t-test with unequal variances.

The lowest number of patients per group that gives at least 80% power is 55. Considering there are four study groups, this comes to a total of N=220 study subjects per group or N=440 total, see figure 3.

Figure 3: sample size calculation.



4. METHODS

7. Study procedures

For the Schedule of Activities listed in tables 1 and 2, a CRF schedule of activities will be prepared and shared with the recruitment sites. A Global Unique Identifier (or equivalent) will be generated and associated with each subject and used for all datasets regarding that subject, e.g., all clinical information, RMT generated data, anonymization procedures.
Clinical information will be collected in the following occasions:

- Main study
    - screening, either by phone or as a visit;
    - baseline visit at the clinic;
    - study-end visit at the clinic;

Up to three phone calls will be performed during the main study and the sub-study, respectively, to monitor the adherence, collect Adverse Events and provide technical support.

4.4.1.Screening

Subjects will be recruited from the Memory Clinics either from an available database (via phone interview), new individuals attending the clinics with interest in the study and the appropriate entry criteria, or following the referral of colleagues, medical institutions or patient advocacy groups. Information critical to assess a subject's eligibility will be collected from the available clinical notes, exams and tests results, the subject medical history and from an interview (by phone or in person) with the subject. In particular, evidence of the following will be sought: (a) diagnosis, (b) positive beta-amyloid biomarkers determined either via CSF or amyloid-PET imaging, (c) Mini-Mental State Examination (MMSE) score and Clinical Dementia Rating (CDR) score obtained 6 months or less before the time of the screening interview, (d) relevant comorbidities that reduce the daily functioning capacities of the subjects, and other information coming from the notes of relevance as entry or exclusion criteria confirmed by MRI. During the interview, other information will be exchanged. For example, a brief motivational introduction for the relevance of this study will be followed by question aimed to understand the interest of the subject to enter into the study, her/his ability to use a smartphone, the agreeability wearing digital devices and having a caregiver/family member/informant interested to support them for the period of the study. If most of the entry criteria are fulfilled, a copy of the Informed Consent Form (ICF) will be sent and/or given to the subjects and to caregiver/family member/ informant some days before the baseline visits and discussed again during the interview. Subjects and caregivers will receive a separate ICF for their respective signature. A specific addendum to the IC will be provided regarding the sub-study with at home monitoring.

4.4.2.Main study, baseline visit

Both the study subjects and informant will be requested to be present at the baseline visit. At the baseline visit, a recap of the eligibility of the subject for the study will be made. Prior to the first data collection procedures, the ICF will be signed by the study subject, caregiver/ informant, and the physician/researcher representing the clinical site. Both the study subject and the caregiver/informant will receive a copy of the signed document.

The following clinical information will be collected either via interview or based on recent (less than 6 months) medical notes or documentation (see table 1 and section 5.1 for a more elaborate description):

- Demographics.
- Medical history.
- Medication use.
- Physical examination (including BMI, vital signs).
- Diet supplement use.
- Godin Leisure-time exercise questionnaire.
- Edinburgh Handedness Inventory Form.
- Smoking habit.
- Drinking habits.
- Blood samples and CSF will be collected for (a) metabolic markers, plasma cholesterol and HbA1S level, (b) genetic analysis and (c) biobanking.

Rating scales rated by physician (or rater) by interviewing the subjects:

- CERAD neuropsychological test batter, including MMSE (as longitudinal assessment)
- Geriatric Depression Scale – short form (GDS)

Rating scale rated by Physician (or rater) by interviewing the caregiver/informant:

- CDR (as longitudinal assessment)
- Amsterdam IADL.
- Alzheimer's Disease Cooperative Study (ADCS) scale:
    - ADL in mild and moderate AD subject subscale, or
    - ADL in MCI subscale for preclinical and prodromal AD subjects
- Neuro Psychiatric Inventory Questionnaire (NPI-Q)

Supervised performance test of the subjects performed at the clinic:

- Physical Functioning Test
    - Gait standard and dual task
    - Timed up-and-go test.

- Spatial memory and navigation task (Altoida Medical Device)

When questionnaires or rating scales are available from the past 6 months, there is no need to fill out the questionnaire again. After completion procedures at the clinic described above, the study participant will receive training for the use of RMT devices in real life, when at home. Briefly, smartphone applications will be installed on their own smartphone of both the subject and caregiver. Each participant will also receive a wrist device and optional, for a brief period, a wearable camera. Caregivers will receive a wrist device as well, if possible with the logistics. A telephone hotline for technical issue will be made available.

4.4.3.Main study, end-of-study visits

The subject and informant will be requested to visit the clinic for an end-of-study visit. Optionally, the Amsterdam IADL scale will be administered with the caregiver/informant, and the CERAD neuropsychological test battery will be repeated with the study subject.

Wearable devices will be recovered and the apps uninstalled from the smartphone. For those subjects that will leave the study, a brief assessment of their health condition will be performed with an interview and they will be dismissed. For those individuals and their caregiver/family member that confirm the interest in joining the sub-study, signature of the ICF for the sub-study will be requested. Arrangement of a date in the following 2-3 weeks for a technical visit at home for feasibility of the installation of the fixed devices. A hot-line for technical assistance will be made accessible via smartphone.

4.4.4.Sub-study, baseline home visits for device installation

During the in-home visit, feasibility for the wiring and installation of the device will be conducted as essential entry criterion by the technical team. Fixed devices will be installed and connected with the WiFi router to monitor activity in various parts of the home, for profiling some social aspects of interpersonal interactions and for more precise sleep-activity patterning. The technical team will take notes on the size and structural features of the house, the household members and other relevant questions, as described in the ICF. Some training about the device characteristics, instructions about the use and location in the house will be performed for the household members. The sub-study will only start when an amendment is approved which specifies the type of device used as fixed sensor in-home.

4.4.5.Sub-study, study-end call or visit

At the end of the time agreed for the sub-study, a phone call will be made to the subject and/ or the caregiver/informant to provide instructions about uninstalling the device and to send

the device back by mail. Alternatively, one representative of the technical team will visit the house and recover the device. Timing is relevant since the same devices will be used again to wire the house of the next participant. A brief survey and few questions about the device use and acceptability will be asked, including AEs or the overall impact of this experience for the subjects and caregiver/informant.

8. RMT/digital technology use in real life

In this study, the presence of an active caregiver/informant is critical for keeping the proper adherence to the study protocol of the subjects and to provide specific information about when a certain ADL is performed by the subject. Caregivers will share some of the same smartphone apps uploaded for the subjects and will receive the same notification, so to help the subject to keep schedule, and may opt for the use of other devices.

2. Main study

The devices included in the study, smartphone applications (aps), were selected according to a series of criteria that minimize the burden to the subjects while delivering information about the time and context in which the ADL is performed. Occasionally, for a few days during the study, the subject will be asked to wear a portable camera that does not broadcast images. Subjects will be instructed: (a) to always keep the smartphone close to them and, when walking outside home, to keep it in a belt holder or trouser pocket and (b) to always wear a wrist-band accelerometer on the dominant hand during the day and for most of the nights.

The following devices will be used:

- The smartphone app Altoida NMI telehealth version, an active interface to collect subject inputs on
    - Orientation, planning skills & spatial memory required for task completion.
    - Executive function skills & prospective memory required for task completion, short and long term.
    - Mood & anxiety
    - Voice & speech analysis
    - Accelerometer, dominant hand - arm movement,
    - Gait and motility at home etc.

4.4.6.Sub-study

Fixed devices will be installed and connected with the WiFi router to monitor activity in the various part of the house, for assessing motility in the various part of the house at various time of the day during specific activities (communicated via smartphone EMA).

1. ASSESMENTS

9. Assessments in the clinic

Demographics

- Date of original informed consent
- Date of birth
- Resident location, e.g. zip code.
- Gender
- Ethnicity
- Referral source
- Education (highest level attained), registered as number of years of formal education.
- Occupation
- Marital status
- Living situation (e.g., lives alone, lives with spouse/partner).
- Handedness, established using the Edinburgh Handedness Inventory Form [6].

Medical history and medication use

- Diabetes or pre-diabetes
- Episodes of depression in adult life.
- Other relevant medical history
- Current medication use, pharmaceutical name and dose

Physical examination

- Body height
- Body weight
- Body Mass Index (BMI) and height will be measured at the baseline visit only.
- Blood pressure measured after the subject has been lying down for 3-5 minutes; following the supine blood pressure, the subject will stand and blood pressure and heart rate will be taken again after 2-3 minutes.

Life habits & AD risk factors

- Diet supplement use, as indicated by the NIH website a series of supplements are commonly used in ageing, even supporting evidence for their benefits in AD are not conclusive (*https://nccih.nih.gov/health/providers/digest/alzheimers*). They are: vitamins B, vitamin E, folate, coconut oil, ginkgo, omega-3 fatty acids/fish oil, vitamins B and E, Asian ginseng, grape seed extract, and curcumin [7].

- Godin Leisure-time exercise questionnaire for assessment how many times a series of different kinds of exercise are performed on average for more than 15 minutes during a typical week [8].
- Smoking habits, including life-time smoking (“when the smoking habit started”) and amount (“how many pack of cigarettes per months were smoked in the last year”).
- Drinking habits. Assessment of alcohol use, expressed in units consumption per day.
- Hobbies, listed as reported number of activities-hobbies / week (i.e., reading, crossword, puzzle solving, listening or playing music, painting, gardening, backing) for how long time (hour/week) [9].

Questionnaires (filled out by study subject)

- *CERAD neuropsychological test battery*: is a well-established assessment [10] that explores the following cognitive dimensions:
    - *Verbal fluency (animal naming)* [11]
    - *15 item Boston Naming Test* [12]
    - *Word list learning [13]*
    - *Word list recall [13]*
    - *Word list recognition [13]*
    - *Constructional praxis*: Rey Complex Figure drawing [14]
    - *Delayed constructional praxis*: Rey Complex Figure recall [14]
- *Mini-Mental State Examination (MMSE).* The MMSE is a 30-item mental status questionnaire that assesses a participant's mental status (orientation, memory, attention, language, visual-spatial abilities, and calculation). A total MMSE score is calculated by summing all correct items out of a possible 30 points. The utility of MMSE, along with global indicators such as CDR, is principally as a clinical descriptor. MMSE was included in the standard clinical assessment as a standard measure that is regularly used in studies and recognized by regulatory authorities [15]. In this study, the MMSE is used longitudinally.
- *Digit Symbol Substitution Test (DSST)* [16] is a neuropsychological performance test that explores attention, working memory and executive functions.
- *Pittsburgh Sleep Quality Index (PSQI)*. The Pittsburgh Sleep Quality Index is a self-rated questionnaire that assesses sleep quality and disturbances over a one-month time interval. Nineteen items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and sleep-related daytime dysfunction. The sum of scores for the seven components gives a global score. The index has adequate internal consistency and high retest reliability, with a diagnostic discriminability of 89.6% sensitivity and 86.5% specificity for good and poor sleepers [17].
- *Epworth Sleepiness Scale (ESS)*. The Epworth Sleepiness Scale is a self-reported questionnaire and it is used to determine the level of daytime sleepiness [18]. A score of 10 or more is considered sleepy. A score of 18 or more is very sleepy.
- *Social Functioning Scale (SFS)*. A questionnaire to assess social functioning, initially developed for schizophrenic patients [19].

- *Geriatric Depression Scale (GDS)* The GDS is a 30-item self-report assessment recorded by the clinician, used to identify depressive symptomatology in the elderly. The GDS questions are answered "yes" or "no". One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0-9 as "normal", 10-19 as "mildly depressed", and 20-30 as "severely depressed". A diagnosis of clinical depression should not be based on GDS results alone. The test has well established reliability and validity with 92% sensitivity and 89% specificity when evaluated against diagnostic criteria. Although a shorter version (15 items) has been validated, the longer version is more likely to have a normal distribution—hence better adapted for use as a dimensional scale—without reliance on theoretical clinical cut-off points. The larger range of items also permits a finer analysis by symptom cluster and not just overall score [20].
- *Test of proficiency in the use of smartphone communication apps.* After all apps will be installed on the smartphone and training for the devices performed, the subjects will be asked to fill a brief questionnaire about which communication apps they are familiar with, e.g., phone calls, SMS messaging, WhatsApp, Facebook, Skype, Instagram, etc.
  The rater will ask the subject to perform some tasks using the smartphone, such as: (a) place a phone call to home; (b) place a phone call to a new number, (c) send an SMS – an agreed short text; (d) start a WhatsApp (or alike app) chat with at least 3 exchanges of conversation with their caregiver that sit in another room; (e) send a picture; (f) read the last arrived email. The rater will score dexterity, self-assurance and efficiency on a VAS (1-5 points).

  The subject and the caregivers will be asked to answer to 4 questions about Smartphone Technology use (score 1-10 with 1 minimum and 10 maximum of agreement): (1) “Using the smartphone, tablet or PC technology enhance my effectiveness for daily activities” , (2) I find these technologies quite easy to use“, (3) “ I feel apprehensive when using these technologies, with sometime fear of making mistakes”; (4) “I have difficulties in concentrating and maintain attention when using these technologies”.

Questionnaires (filled out by caregiver/study partner)

- *The Amsterdam-IADL (A-IADL) questionnaire short version*. This questionnaire consists of 30 questions that explore the functional capacity during daily living activities as observed in the subjects during the last week. The questionnaire includes several questions regarding the use of media and devices [22]. It is scored by the caregiver/ family member, can be operated on tablet or PCs and will take 10 minutes to fill in. (www.alzheimercentrum.nl/professionals/amsterdam-iadl/).

- *Clinical Dementia Rating (CDR)*. The CDR is comprised of a semi structured interview one with the with a caregiver. During the interview, the rater assesses the participant's current status in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) and rated accordingly using a 5-point scale (0 = no impairment, 0.5 = questionable impairment, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia, http://knightadrc.wustl.edu/cdr/aboutcdr.htm). The outcome measures of the CDR and CSD-SB are CDR scores (derived from an algorithm developed by the Knight ADRC) [23].
- *Alzheimer's Disease Cooperative Study (ADCS) scale*. ADL in mild and moderate AD subject subscale. A questionnaire describing the performance of activities of daily living in patients with Alzheimer's Disease [24]. ADL in MCI subscale for preclinical and prodromal AD subjects. A questionnaire describing the performance of activities of daily living in patients with mild cognitive impairment [25].
- *Neuro Psychiatric Inventory Questionnaire (NPI-Q)*. A questionnaire to assess 12 neuropsychiatric disturbances, e.g. irratability and depression, in dementia patients [26]. This questionnaire is filled out by a caregiver of informant. All 12 items are scores on severity and frequency.

Performance test at the clinic

- *Navigation and Spatial memory test:*
  - Altoida medical Device test is based on two augmented reality gamified tasks that run on iPAD tablets. In the first task virtual objects (e.g., teddy bears) appearing on the video image captured by the iPAD active camera will be hidden in some specific part of the room and need to be retrieved some minute afterward. A second test require to navigate through the room by watching in the images of the environment transmitted by the camera of the iPAD while a virtual situation of danger and stress (e.g., fire alarm on in the room) is simulated. The execution of these tests requires an active functional engagement of several cognitive dimensions and is captured by the iPAD sensors every seconds. The duration is typically about 15 minutes.
- *Physical functioning tests:*
  - *One minute walking test (1MWT).* Participants are instructed to walk at a self-chosen comfortable pace for 1 minute through a hallway of 30-50 meters, while wearing validated accelerometers and gyroscopes (Physilog 6, see description below).
  - *One minute dual walking test (1MDT).* Participants are instructed to walk at a self-chosen comfortable pace for 1 minute through a hallway of 30-50 meters, while wearing validated accelerometers and gyroscopes (Physilog 6, see description below). In addition, participants are instructed to count backwards from 100 in steps of 7 out loud.

- *Instrumented Timed Up and Go (TUG) Test.* Timed Up and Go is a measure of functional lower limb muscle strength that is useful in quantifying functional change of transition movements where subject begins in a seated position, stands up completely, then returns to the sitting position [29]. During this test, subjects will wear a validated accelerometer and gyroscope (Physilog 6, see description below). The duration of the test is about 10 min including the setting of the device.

10. Digital technology Assessments

- *Altoida Medical Device:* Altoida (https://altoida.com/) is a mobile phone and tablet-based digital biomarker platform that detects early and subtle micro-errors (accuracy) and micro-movements (latency), which has been shown to be useful in detecting MCI that will progress to dementia years in advance. Using a user-friendly exercise that simulates a complex activity of daily living, the Altoida's Neuro Motor Index (NMI), a score derived from the performance combining data streams from: voice data, hands micromovements and micro-errors, gait micro-errors, posture changes, eye tracking, visuospatial navigation micro-errors etc, provides individually tailored prognostic information with the greatest ecological validity and scalability. Altoida's NMI Medical Device has received DA class II medical device qualification from FDA for the evaluation of perceptual, memory and functional impairment relevant for Activities of Daily living (ADL) and for assisting the diagnosis of MCI & AD in subjects between 55 and 95 years of age. NMI showed a diagnostic accuracy of 94% in predicting cognitive worsening in amyloid positive individuals who converted at MCI due to AD after 5 years [30].

Study teams will be provided with a detailed study operations manual describing the data collection steps for each in-clinic test described above in sections 5.1 and 5.2.

11. Withdrawal of individual subjects

Subjects can withdraw from study participation at any time for any reason if they wish to do so without any consequences. The principle investigator can decide to withdraw a subject from the study for urgent medical reasons.

12. Replacement of individual subjects after withdrawal

Subjects will be replaced in case of withdrawal within 4 weeks after the baseline assessment.

13. Follow-up of subjects withdrawn from treatment

In case of withdrawal, subjects will be asked for their reason for withdrawal. However, they are not obliged to provide a reason for their withdrawal.

14. Premature termination of the study

There are no specific criteria for premature termination of the study.

5. SAFETY REPORTING

Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

15. AEs, SAEs and SUSARs

5.5.1.Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to a RMT device. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

5.5.2.Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs to the accredited MREC that approved the protocol within 15 days after the sponsor has first knowledge of the serious adverse reactions. Only SAEs that occur within one month after the examinations at baseline and follow-up will be reported. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

All (S)AE's that occur within 24 hours of administration of the GE imaging agent, regardless of assessment of relatedness will be reported to GEHC. After this safety period of 24 hours, only adverse events that are considered related to the tracer will be reported to GEHC.

5.5.3.Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

16. Data Safety Monitoring Board (DSMB) / Safety Committee

N/A

6. STATISTICAL ANALYSIS

Data obtained from RMTs will be either continuous (as, for example, accelerometer recording having several samples per second, participant's relative locations recorded via GPS every 5 minutes, ….) or obtained during a single clinical visit only (as, for example, gait assessment).
Continuous raw data will be analytically processed and features characterizing behaviour per day will be obtained. For example, actigraphy read-outs will be used to derive sleep characteristics using Cole-Kripke algorithm (duration, quality of sleep, etc.) for every night, relative location data will be used to estimate distance travelled per day, duration of home stay per day, number of places visit per day and so on. Complete strategy for handling multi-sensor data and list of relevant features will be developed through the project duration. At the end, RMT data will be either a day-by-day time series or obtained at a single study time point.
We will analyse each RMT measurement separately, characterizing they variance to assess, whether 1) they are different between following groups: (a) healthy volunteers and (b) subjects with preclinical AD, (c) subjects with MCI due to AD, and (d) subjects with mild-to-moderate AD dementia, and 2) whether they are related to standard clinical questionnaires for ADL. For a continuous day-by-day time series, we will model such a RMT measure using a mixed-effect model for repeated measures (MMRM) based on observed case data. The model will include study group (or a related ADL scale), age, sex, and other related covariates/factors. Strength of between study groups difference (or relation to related ADL scale) is of primary interest. The within-participant covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate participant random effect. Weekdays and weekends time

series will be analyzed separately. For the case of RMT assessed only once per study at clinical visit (as gait assessment), analysis of covariance (ANCOVA) will be conducted. Namely, an RMT will be used as a dependent variable, whereas study group (or related ADL scale), age, sex, and other related covariates/factors will be included in the model. Correction for multiple comparison will be considered for univariate RMT modeling.

As a second step, we will try to answer the question, whether combination of different RMT assessments contributes to either study group discrimination and/or is related to ADL scale in a multivariate predictive modeling approach. Results of univariate modeling (described above) will be considered as a filter-based feature selection, which informs us on what information to include into the model. Continuous RMT data will be aggregated (as mean, standard deviation, lagged autocorrelation, … estimated using data from a whole 8-week experiment duration) for each participant. These preselected aggregated features in combination with preselected RMT measures obtained at a single study point will be used for modeling. Under assumption that data are missing at random, multiple imputation will be applied for covariates, where missingness is not drastically high. Multivariate prediction (of either study group or related ADL scale) models will be constructed and further variable selection, based on, for example, LASSO L1-regularization for (generalized) linear models, or different feature selection algorithms will be applied. Models' performance will be characterized through the cross-validation.

For the assessments, which will be primary done at the clinic and repeated at home (as, for example, experiments with the Altoida app), results will be compared using Bland Altman analysis to assess the agreement between two quantitative variables. Based on the result, recommendation regarding possibility to use home-based tests will be provided. To check, whether 'real-world' (at home) assessment is beneficial to the one done in the 'clinical environment', we will check, whether the predictive models (described above) using 'home' assessments have better predictive performance, than the ones, using 'clinical' assessments.

7. ETHICAL CONSIDERATIONS

17. Regulation statement

The study will be carried out in accordance with the ethical conduct and juridical laws of the *Declaration of Helsinki* 59th WMA General Assembly, Seoul, October 2008, (www.wma.net), and in accordance with the GDPR regulations and WMO.

18. Recruitment and consent

Supervising doctors and researchers at the research sites will screen participants for eligibility. If eligible the candidate will be informed orally and in writing (i.e. an information letter) about the study and asked to participate. The aim of the study and the procedure will be explained to the participant. Participants are informed that they can withdraw from the

study at any point of the study without any consequences. It is made clear that withdrawal from the study will not affect further treatment or legal rights. The participant will have a sufficient amount of time (i.e. at least 7 days) before making a decision about involvement in the study. Subsequently, the participant is asked to sign an informed consent form according to the national guidelines. After the informed consent is signed, data will be collected during the baseline visit. All materials will be used according to national ethical guidelines for Good Clinical Practice.

19. Objection by minors or incapacitated subjects

The minimal MMSE score for participation is 17, which means that no incapacitated subjects are allowed to participate in the study.

20. Benefits and risks assessment, group relatedness

Benefits:

There is no direct benefit for the participant. This study may lead to the discovery of early diagnostic and prognostic markers and novel treatment targets for Alzheimer's disease, which will be a benefit for future patients with AD.

Risks:

Neurophysiological testing might be tiresome. The RMTs have to be used every day, which might lead to discomfort.

21. Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

22. Incentives

Participants in the study will receive reimbursement for their travel expenses when completing a study visit.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

23. Handling and storage of data and documents

All clinical-and personal data (age, gender, level of education, clinical data, and diagnosis) will be provided with a code which cannot be related to an individual. Any information that can be used to potentially identify an individual will not be included in the research database. Data will be available to partners of the ANANEOS JOINT COLLABORATION AGREEMENT in accordance with the DATA SHARING AND PROCESSING PROTOCOL. All data will be centrally stored in a platform that was developed in ANANEOS and that will be adapted for the specific needs of the ANANEOS project.

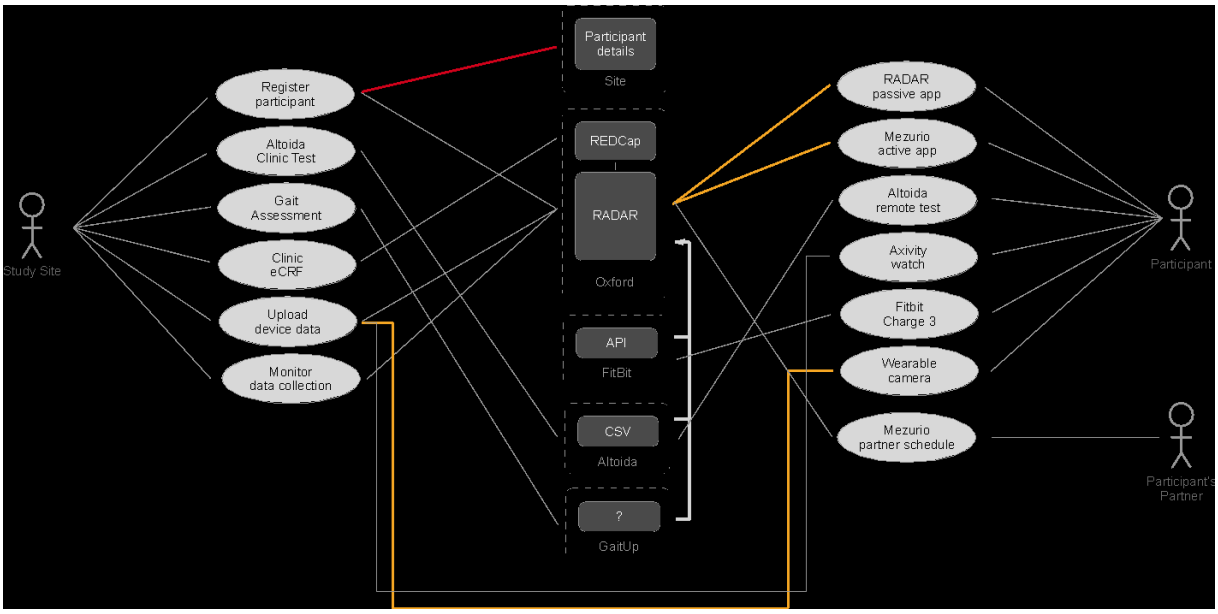
Participants privacy and confidentiality will be respected throughout the course of the study. Anonymised data will be encrypted and transferred via internet and Bluetooth connections to secure servers managed by each local site. Each participant will be assigned a sequential identification number, used to collect, store, and report participant information. Identifiable information will be stored within a password protected eCRF, disjoint from the ANANEOS platform, accessible only to members of the immediate research team. The identification number will be common across the eCRF and ANANEOS platform.

Data collected via the wrist-worn wearable devices (i.e. Axivity AX3, FitBit Charge 3) is first transmitted to respective company data warehouse from which data be accessed, encrypted and uploaded to a secure server maintained by the sponsor organisation, and will be not identifiable by patient name. Data collected via the smartphone will be encrypted and uploaded to secure servers by Wi-Fi or mobile data connection. Data will be temporarily cached on the smartphone until an appropriate connection is available and will then automatically deleted from the phone memory.

The research team will keep legible and accurate documents to ensure thorough documentation of study conduct. The highest degree of confidentiality will be maintained for managing data collected throughout the course of this study, however, to meet legal responsibilities and quality assurance policies, the investigational site will permit authorised representatives of the sponsor, funder and health authorities to examine anonymised records to satisfy quality assurance reviews, audits and evaluations of study safety and progress.

The non-identifiable data acquired may be transmitted through a computer network, through the internet, or transferred via removable media to be shared with other members of the RADAR-AD consortium. This information will be anonymised and will not include anything that could identify patients by name, date of birth or address. Patients will be informed and asked to consent to sharing of information.

Figure 4 provides a schematic overview of the data flow within the study.



24. Monitoring and Quality Assurance

This is a multisite study, in which all partners have been chosen based on expertise. Coordinators will be appointed for each site. These coordinators are responsible for a successful dissemination of the protocols among laboratories and clinical centres involved in the evaluation of cognitively normal elderly individuals.

25. Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. Non-substantial amendments will not be notified to the accredited METC and the competent authority (CA) but will be recorded and filed by the sponsor.

26. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

27. Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days,

including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

28. Public disclosure and publication policy

In accordance with the statement publication policy, all subjects may assume that the research in which they participated is executed in a competent and objective way. Results will be published in peer-reviewed scientific journals. Negative results will also be published.

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