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Pilot Operation Manual

CAREGIVERSPRO-MMD PROJECT

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Project Number	690211	**Acronym**	CAREGIVERSPRO-MMD
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Project coordinator	Universitat Politècnica de Catalunya - BarcelonaTech Prof. Ulises Cortés, ia@cs.upc.edu		
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1.0	31-08-2016	Final	FUB	Final version

Executive summary:

D4.1 is the first deliverable of WP4, aimed to develop the methodology to be used along the recruitment period, the pilot stage and the data analysis. In order to ensure that all pilots operate in the same way, we will define a Pilot Operation Manual, which all pilot sites will commit to follow. FUB will be the main contributor of this document for clinical aspects receiving the support, feedback and agreement from the rest of pilots. This document contains:

- General description of the study design and the pilot composition
- Define the inclusion and exclusion criteria
- User recruitment methodology best practices
- Ethical documentation preparation (Informed Consent Forms, Information Sheet, authorisations for collection and processing of personal data, etc.)
- Definition of the standard user assessment
- Schedule of the user assessment along the pilot
- Summary of the minimum data to be collected by CAREGIVERSPRO-MMD
- Schedule for data collection
- Schedule for data analyses

Table of content

1 Acronyms

AD	Alzheimer's disease
ADRQL	Alzheimer’s Disease Related Quality of Life
BADL	Barthel ADL Index / Barthel Index of Activities of Daily Living
C-MMD	CAREGIVERSPRO-MMD
C-MMD-USE	CAREGIVERSPRO-MMD User Satisfaction Scale
CDR	Clinical Dementia Rating
CG	Caregiver
CRO	Clinical research organization
DAS	Dyadic Adjustment Scale
DSM	Diagnostic and Statistical Manual
FS	Flourishing Scale
GDS	Geriatric Depression Scale
IADL	Lawton Instrumental Activities of Daily Living Scale
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICT	Information and communications technology
INB	Incremental net benefit
ISCED	International Standard Classification of Education
ISCO	International Standard Classification of Occupations

KSS	Kuppuswamy's Socioeconomic Scale
MCI	Mild Cognitive Impairment
MMAS-8	8-item Morisky Medication Adherence Scale
MMSE	Mini-Mental State Examination
MRRC	Memory Resource and Research Centres
MSPSS	Multidimensional Scale of Perceived Social Support
NICT	New Information and Communication Technologies
NPI	NeuroPsychiatric Inventory
OECD	Economic Co-operation and Development
PDC	Proportion of days covered
PLWD	People Living with Dementia
QoL	Quality of life
RUD	Resource Utilization in Dementia
SES	Socioeconomic status
SF-36v2	Medical Outcomes Study (MOS) 36-Item Short Form 2nd version
STAI	State Trait Anxiety Inventory
WHO	World Health Organization
WHO-DD	World Health Organization's Drug Dictionary
WHOART	WHO Adverse Reactions Terminology
ZBI	Zarit Burden Interview

2 Synopsis

Study title	"Multicentre pilot study to determine the benefits of CAREGIVERSPRO-MMD platform use based on the information and communications technology (ICT), dedicated to the support and assistance of dyads living with neurocognitive diseases including persons living with mild cognitive impairment or mild to moderate dementia and their primary caregivers" Project: "Self-management interventions and mutual assistance community services, helping people living with dementia and caregivers connect with others for evaluation, support and inspiration to improve the care experience"
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Promotor	**Universitat Politècnica de Catalunya (UPC) - Barcelona Tech** Prof. Ulises Cortés - C/Jordi Girona, 1-3 - UPC, Campus Nord, Omega building - Catalonia, Barcelona, 08034 - Offices 201 to 207, 2nd floor ia@cs.upc.edu - Phone: +34 934137842 European Union's Horizon 2020 research and innovation programme under grant agreement No 690211
Study design	Prospective, randomised, multicenter, controlled, parallel and longitudinal study.
Population and sample	Dyads: People living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers.

[1] **Text marked in yellow and red, is to be completed by each particular instance of this protocol with data from each pilot site** (XXX)

Hypothesis of the study	**Primary hypothesis** • The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the dyad, in the subjective quality of life of persons living with mild cognitive impairment or dementia (mild to moderate dementia) and in the level of burden experienced by the primary caregiver. **Secondary hypothesis** • The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the persons living with mild cognitive impairment or dementia (mild to moderate dementia), in their treatment adherence, behavioural and psychological symptoms and use of psychotropic drugs. • The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the persons living with mild cognitive impairment or dementia (mild to moderate dementia), in their activities of daily living and psychological and neuropsychiatric disorders. • The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the primary caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in psychological and neuropsychiatric disorders. • The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the primary caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in perceived social support, success in relationships, self-esteem, purpose and optimism. • The use during 18 months of CAREGIVERSPRO-MMD platform improves treatment adherence for the dyad (persons living with mild cognitive impairment or dementia (mild to moderate dementia) and their primary caregivers. • The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the dyad (persons living with mild cognitive impairment or dementia (mild to moderate dementia) and their primary caregivers), in the quality of the caregiving relationship. • The use during 18 months of CAREGIVERSPRO-MMD platform reduces total costs of care (direct and indirect costs) for the dyad (persons living with mild cognitive impairment or dementia (mild to moderate dementia) and their primary caregivers. • The use during 18 months of CAREGIVERSPRO-MMD platform reduces total number of hospitalisations for the persons living with mild cognitive impairment or dementia (mild to moderate dementia).
objectives of the study	**Primary objectives** • For persons living with mild cognitive impairment or dementia (mild to moderate dementia): to evaluate their subjective quality of life in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months. • For primary caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia): to evaluate their perceived burden in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months. **Secondary objectives**

Secondary objectives related to persons with MCI or PLWD

- To evaluate the activities of daily living for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the treatment adherence for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify an improvement from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the behavioural and psychological symptoms for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the neuropsychological functioning of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the total number of hospitalisations for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

Secondary objectives related to primary caregivers

- To evaluate the subjective quality of life for caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the treatment adherence for caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify an improvement from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the behavioural and psychological health and wellbeing of caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the perceived social support, success in relationships, self-esteem, purpose and optimism to caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.
- To evaluate the use of psychotropic drugs for caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

Secondary objectives related to dyad

- To evaluate the quality of caregiving relationship between caregiver and persons living with mild cognitive impairment or dementia (mild to moderate dementia) in dyads, in order to identify a benefit from use of the CAREGIVERSPRO-MMD

	platform during 18 months. **Secondary objectives related to economic and financial benefits** ● To evaluate the direct and indirect costs of care to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months. **Secondary objectives related to CAREGIVERSPRO-MMD platform users** ● To evaluate the degree of satisfaction of use of the CAREGIVERSPRO-MMD platform during 18 months.
Inclusion criteria	**For persons living with mild cognitive impairment or dementia** ● People, aged 50 and over, living in the community, who are able to give informed consent (or the legal tutor). ● Diagnosed with mild cognitive impairment (MCI) according to Petersen criteria [Albert et al, 2011] or mild to moderate dementia diagnosed according on DSM-IV criteria (Diagnostic and Statistical Manual, 4th edition) [American Psychiatric Association, 1994]. ● Having a Clinical Dementia Rating (CDR) of 0.5 for MCI, 1-2 for mild to moderate dementia. ● Having a Mini-Mental Exam score (MMSE) [Folstein et al, 1975] between 30 and 25 (inclusive) for MCI, and between 24 and 10 (inclusive) for dementia. ● Having a primary caregiver, familiar (or not), informal (or not) identified and also included in the study. ● Be willing to use Information Technology and Communications (ICT) according to the investigator criteria. **For primary caregivers** ● People, aged 18 years and over, with no diagnosis or no evidence of mild cognitive impairment or mild to moderate dementia (according DSM-IV criteria) [American Psychiatric Association, 1994], who are able to give informed consent and with an intention to complete the study. ● Primary caregivers, informal (or not), familiar (or not), of person with mild cognitive impairment or mild to moderate dementia. ● People with Internet access and basic knowledge and skills in managing internet and social networks, or keen to learn, according to the investigator criteria. ● Having a Geriatric Depression Scale (GDS-Yesavage - 15 items) score less than 11 at the time of entry into the trial indicating no severe depressive symptoms. ● Having no specific conditions (evaluated by the investigator) reducing their physical abilities below the norm for their age that would limit or impair CAREGIVERSPRO-MMD platform use. ● Be willing to use Information Technology and Communications (ICT) according to the investigator criteria.
Exclusion criteria	**For persons with mild cognitive impairment and people living with dementia**

	• Terminal or severe illness with survival prognosis less than 18 months. • Having delusions, hallucinations, behavioural disturbances, that may interfere with the use of Information and Communications Technology (ICT) tools. • Relevant sensory problems (visual or hearing impairment) or motor disability (such as paralysis of upper limb or disabling arthritis or disabling tremor, etc...) evaluated by the investigator that would interfere with the use of Information and Communications Technology (ICT) tools. • Not speaking the language of the country where the pilot is being conducted. **For primary caregivers** • Terminal or severe illness with survival prognosis less than 18 months. • Relevant sensory problems (visual or hearing impairment) or motor disability (such as paralysis of upper limb or disabling arthritis or disabling tremor, etc...) evaluated by the investigator that would interfere with the use of Information and Communications Technology (ICT) tools. • Not speaking the language of the country where the pilot is being conducted.
Study exit criteria	• If the primary caregiver changes or if the caregiver can't continue his role of caregiver. • Primary caregiver who do not use the platform during 2 months due to a justifiable reason according to the investigator criteria. • Primary caregivers showing malicious or inappropriate CAREGIVERSPRO-MMD platform use according to the investigator criteria. • Severe illness for the persons living with mild cognitive impairment or dementia (mild to moderate) or their caregivers evaluated by the investigator that interfere with the ability or potential to use Information and Communications Technology (ICT) tools. • One member of the dyad wants to retire informed consent and wants to withdraw from the study. • Hospitalisation or institutionalisation >2 months not related to the role of care.

Parameters to be evaluated	**Screening**
	• **For people with mild cognitive impairment (MCI) or dementia (PLWD) and their caregivers:**
	  ○ Sociodemographic variables
	  ○ Comorbidity
	  ○ Medications
	  ○ Concomitant treatments
	  ○ Cognitive-Clinical symptoms
	• **For primary caregivers:**
	  ○ Depression
	
	Primary outcomes
	• **For MCI and PLWD**
	  ○ Subjective quality of life

	• **For primary caregivers**
	  ○ Perceived burden
	
	Secondary outcomes
	• **For MCI or PLWD and their caregivers:**
	  ○ Physical health
	  ○ Medication and concomitant treatments
	  ○ Comorbidity
	  ○ Adverse events
	  ○ Treatment adherence
	• **For MCI or PLWD:**
	  ○ Cognitive-Clinical symptoms
	  ○ Activities of daily living
	  ○ Behavioural and cognitive symptoms
	  ○ Depression
	• **For primary caregivers:**
	  ○ Subjective quality of life
	  ○ Depression
	  ○ Anxiety
	  ○ Perceived social support, success in relationships, self-esteem, purpose and optimism
	• **For dyads**
	  ○ Social relationship of the dyad
	• **For CAREGIVERSPRO-MMD platform users**
	  ○ Satisfaction
	  ○ Platform use
	• **Economic variables**
	  ○ Resource utilization
	  ○ Direct and indirect costs of care

Intervention strategy	Intervention group using the platform "CAREGIVERSPRO-MMD" platform versus control group.
Sample included in the study	602 dyads: - Intervention group: 301 dyads (person with mild cognitive impairment or person living with dementia and his primary caregiver). - Control Group: 301 dyads (person with mild cognitive impairment or person living with dementia and his primary caregiver).
Sample included in the local study	201 dyads: - Intervention group: 101 dyads (person with mild cognitive impairment or person living with mild or moderate dementia and his primary caregiver). - Control Group: 101 dyads (person with mild cognitive impairment or person living with mild or moderate dementia and his primary caregiver).

Number of clinical research teams involved	1. University of Hull (United Kingdom) 2. COOSS Marche (Italy) 3. Rouen University Hospital (France) 4. Fundació Universitària del Bages (FUB) - UVic-UCC (Spain)
Number of local clinical research centers involved	- Fundació Sociosanitaria de Manresa (FSSM) - Associació de Familiars d'Alzheimer de Manresa i Comarca del Bages
Statistical analysis	**Primary analysis:** Change in PLWD QoL (ADRQL) and caregiver burden (ZBI score) defined as difference between 18 months value and baseline value will be compared between groups fitting an analysis of covariance.. **Secondary analysis related to people living with mild cognitive impairment and living with dementia and their caregiver** Comparisons at 18 months of IADL score will be done fitting a polytomous logistic regression. Comparisons of proportions of people living with dementia who reduce ⩾3 points in Mini Mental at 18 months between groups will be done computing the confidence interval for the estimate of difference. Differences in SF-36v2 PCS and MCS component summary measures will be performed according to Quality Metric's Health Outcomes ™ Scoring Software 5.0 available. Comparison of NPI questionnaire at 18 months will be performed fitting a polytomous logistic regression with group as independent variable. Comparisons of proportions of caregivers using psychotropic drugs between groups will be done computing the confidence interval for the estimate of difference.. The rate of change comparisons between groups of ZBI and ADRQL will be assessed fitting a random coefficient model. IADL score and NPI questionnaire will be fitted with a two populations polytomous response for repeated measures. A rank analysis of covariance combined with Cochran-Mantel-Haenszel statistics will also be fitted to evaluate differences between groups for other non-centered scores. Treatment adherence will be compared using the proportion of days covered (PDC) Comparisons at 18 months of DAS and MSPSS score will be done computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. A rank analysis of covariance combined with Cochran-Mantel-Haenszel statistics will also be fitted to evaluate differences between groups. MMAS-8 will be fitted with a two populations polytomous response for repeated measures. Overall efficiency savings to family and costs associated in both people living with dementia and caregivers will be done computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. Overall efficiency savings will be performed in the same way. Comparison of median time to institutionalisation will be done computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. Exploratory cost-effectiveness analysis of the platform related to caregivers will be performed computing incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB).
Implementation schedule	Duration of recruitment and information period: 4 months [From January 2017 to April 2017]. Duration of randomization and data collection: 18 months [From April 2017 to September 2018].

	Number of scheduled medical visits: ● 1 Session of training on CAREGIVERSPRO-MMD platform for the intervention group after randomization. ● 1 Research visit every 6 months for both groups of dyads. Total duration: from the first dyad inclusion until the last visit of the last dyad: 22 months Duration of data analysis statistical report and clinical report: 14 months [From October 2017 to October 2018]. Duration of dissemination of study results: 4 months [From September 2018 to December 2018].

3 Abstract

According to the World Health Organisation [WHO, 2015] there are 46.8 million people living with some form of dementia worldwide for which there is currently no treatment or effective strategy that can halt or reverse their progressive cognitive impairment. As Europe's population is aging, and longevity is the main risk factor for developing dementia, long-term care for older citizens will represent an increasing financial cost for society. There are currently 19 million people living with dementia in Europe, and this figure is expected to reach 31.5 million by 2050. To manage this transition, health policies of the EU and its member states are focused on enhancing elderly people's longevity and preventing their dependency. This has the double aim of increasing their subjective quality of life while reducing costs and increasing the effectiveness of healthcare. That is why the European project "CAREGIVERSPRO-MMD" (RIA, PHC-25-2015, PIC: 690211), with participating partners: the Universitat Politècnica de Catalunya (UPC), MobilesDynamics (MDA), University of Hull (HUL), Q-Plan International LTD (QPL), COOSS Marche (COO), Fundació Universitària del Bages (FUB), Rouen University Hospital (CHU) and the Centre for Research and Technology Hellas (CERTH), aims at evaluating the web platform "CAREGIVERSPRO-MMD", accessible for computers, phones and tablets, and defined as an mHealth application specifically for caregivers and people living with mild cognitive impairment or mild to moderate dementia, which will provide value-added services based on social networks, tailored interventions, clinical strategies and gamification to improve the subjective quality of life of those living with cognitive impairment or dementia as well as that of their caregivers (dyads), thus supporting them to live in the community for as long as possible.

In order to evaluate the effectiveness and impact of the platform in people living with mild cognitive impairment or dementia (mild to moderate) together with their caregivers, a prospective, randomised, multicenter, controlled, parallel and longitudinal study was devised with 602 dyads (carried out in a multicentre study: 100 followed by HUL, 200 by COO, 202 by FUB and 100 by CHU), divided into two groups of equal numbers. The groups will be comprised of one "intervention" group with access to the platform and another "control" group without any access to it. During the following eighteen months, aspects related to the individuals' health (general health, neuropsychological functioning, activities of daily living, subjective quality of life, adherence to pharmacological treatment and comorbidities), social aspects (cohesion of the dyad, social support, success in relationships, self-esteem, purpose and optimism) and economic aspects (cost-effectiveness of the use of the platform) and the degree of satisfaction and usability of the platform by all users will be evaluated.

4 Introduction and background Information

4.1 The population profile associated with dementia in Europe

According to the Organisation for Economic Co-operation and Development [OECD, 2013], in its report Health at a Glance, life expectancy has increased significantly in Europe (by 10 years in the last half century) to reach the age of 80.1 years in 2013. Topping the statistics: Italy (82.7 years), followed by Spain (82.4 years), France (82.2 years) and the United Kingdom (81.1 years) [OECD, 2013]. In parallel, the Statistical Office of the European Commission [Eurostat, 2013] published population statistics revealing that the average age of Europeans has already reached the figure of 41.2, with people under 14 years old representing 15.6% of the population and people of working age (15 to 64 years) making up 66.9%. The remaining 17.5% are aged 65 years old or older and about 4.8% are over 80 years old, a figure which reaches 6% in Italy (the highest value). All these figures demonstrate that the European population has aged considerably over the last 10 years, with two significant factors coinciding in a short time: on the one hand longevity is increasing, and on the other hand there is a low fertility rate of 1.5 births per woman per year [Eurostat, 2013].

Europe's ageing population has led to an increase in age-related diseases (cardiovascular diseases, cancer, diabetes, Parkinson disease, osteoporosis...), especially, dementia. According to the analysis of several epidemiological studies in Europe on the prevalence of dementia, carried out by the European Collaboration on Dementia [EuroCoDe, 2013] prevalence working group of the organisation "Alzheimer Europe", there are currently 6.36 million people over the age of 65 living with various neurodegenerative diseases, a figure that could exceed 10 million people in 2040. In this context of neurodegenerative diseases, Alzheimer's disease is the most common type of dementia, representing between 50% and 60% of all dementias diagnosed, causing memory loss, decline in brain function and personality changes, directly affecting the executive functions of the person and impacting their work and social life [Gironès et al, 2002]. Because of the number of people living with Alzheimer's disease, the number of family caregivers which provide care and support is around 20 million (about 3 people per person with dementia).

4.2 The "Alzheimer Europe" Paris Declaration

As a result of the growing concern about the significant consequences of dementia, institutions such as “Alzheimer Europe” (alzheimer-europe.org) are trying a gain a better understanding of population needs, issuing warnings to organisations and institutions of the European Union, the World Health Organization, the Council of Europe and European national governments on the need to act urgently.

In the “Paris Declaration” [Alzheimer Europe, 2009], experts linked to Alzheimer Europe called on European and national policy makers to give Alzheimer's disease and other forms of dementia both the political and public health priority they deserve, putting forward various proposals in the fields of research and medicine, healthcare and social support and ethics and law.

The most important points to consider are the following ones:

- People with dementia and their caregivers need actions and tools that cover all aspects of their care and support needs and that are tailored to the specific needs of each stage of the illness.

- Caring for people with dementia can have a significant impact on the subjective quality of life of caregivers. Consequently, it is necessary to promote active policies for the recognition of potential significant burden of caregivers of people with dementia and promote the support and development of adequate support services and help.

Therefore, Alzheimer Europe recommends fostering initiatives which truly support the caregiver, since in practice, this will directly result in a better quality of life for people with dementia [Alzheimer Europe, 2009]. By definition, primary caregivers are those people who, being a relative or not of the person with dementia, are in closest human contact with them. Their main task is to meet the physical and emotional daily needs of the person. They also keep the person connected with society and are affectionate with the person as they empathise with their experiences. Caregivers’ work takes on a great significance for other people in the person’s circle as the illness progresses, because as well as providing direct care, they also take on an important role in the reorganisation, maintenance and cohesion of the group around the person living with dementia [Astudillo et al, 2010].

4.3 The aim of European Health Policy: To give support and respite to non-professional caregivers

In Europe, one important objective of health policy is to foster and maintain networks of non-professional care of people living with dementia. This objective can be achieved through economic support to people living with dementia with difficulties in performing activities of daily living, in order to encourage the use of a professional service and therefore ease the burden of the non-professional caregiver. Given the reality that non-professional care accounts for over 80% of the total use of non-medical care; it is essential to identify strategies associated with giving respites and support for caregivers so that they will be less likely to seek for residential care, with consequent savings in public and private healthcare spending [Rapp et al, 2011].

The European health plans have put forward measures to improve care for people living with dementia with a more personalised and tailored approach aimed at both people living with dementia and their caregivers' needs. The main goal is to implement an integration process through an active and participatory network in the care of people with dementia, giving both assistance and support. This model should include tools and mechanisms to improve the process of comprehensive care, in particular, case management for older people in complex situations and the necessary resources provided to their caregivers. In this way, this aim could move on from just focusing on medical treatment for dementia to work towards the comprehensive and holistic care of both those living with dementia as well as their families and caregivers. This approach could concentrate its efforts on improving understanding and care and in this context, the caregiver is a key part of the process [Pimouguet et al, 2013].

Numerous studies on caregivers providing support to people living with neurodegenerative diseases postulate that the role of caregiver is vital in the monitoring and reporting of symptoms and the effects of the individual therapeutic interventions. It is therefore very important to establish an effective therapeutic alliance between the health system and caregivers in the medical management of the person living with dementia [Jicha, 2011]. In this context, support for creating tools that foster this relationship would be in line with improved information flow between those living with dementia, healthcare and medical teams, caregivers and family members.

4.4 Attention and follow-up of the caregiver: A crucial part in providing support.

People living with dementia are likely to need different degrees of assistance and help in their daily lives during the various stages of the disease's progression, especially when it

begins to progress to a more advanced stage. Daily assistance may come from various sources, both from clinical staff as well as from members of the family. It has been found that if the primary caregiver is the spouse or a child of the person, they have to cope with a significant level of responsibility. Consequently, the effects on the caregiver's health and daily life may result in sleep disturbance, anxiety, depression and stress that could end up affecting the caregiver's quality of life and endangering their own health and wellbeing [Callan et al, 2009; Varela et al, 2011].

Thus, non-professional caregivers of people living with dementia are often under a lot of pressure and have increased risks of suffering physical and psychiatric illnesses. In this regard, providing caregivers with medical and healthcare knowledge concerning dementia and the necessary tools and/or support to cope with stress would bring rewards for both the caregiver and the people living with dementia as far as quality of life and health monitoring are concerned [Cheng et al, 2012].

In this context, family caregivers should assess their well-being and quality of life when dementia is diagnosed, in order to keep track of these and meet the challenges of the illness progression with the proper and adequate tools [Välimäki et al, 2012]. There are many risk factors associated. Caring for someone living with dementia is linked to an increase in depressive symptoms, with 50% of caregivers reporting symptoms of depression within 2-3 years of caregiving [Joling et al, 2010], and an increased risk of cardiovascular disease, and it has been shown that the right intervention in the caregiver's lifestyle can decrease depression and improve their overall health [Moore et al, 2013]. Studies which have focused on the analysis of health monitoring of caregivers have always reported a deterioration of physical and mental health of this group, with a common occurrence of family conflicts and even suicide after the death of the person being looked after [Shaji et al. 2003].

Recent systematic reviews on the subject suggest that there is evidence to show that support interventions for the caregiver can help reduce their psychological distress as well as improving other aspects of their health and wellbeing. These findings recommend that doctors involved in the monitoring of people living with dementia should investigate and ask caregivers about their concerns and questions as a strategy for improving the people living with dementia health. The information contained in their answers will be of great interest and support for creating the best assistance plan [see Candy et al, 2011].

4.5 The unmet needs of caregivers

The ageing in population in the european society will bring an increase in the number of people with dementia living in our community. This will lead to an increased demand for care and welfare services in order to provide efficient and personalised assistance, which

requires a thorough understanding of subjective and objective needs. Dementia is currently an incurable illness and its treatment requires a careful approach involving both people living with dementia and their families. In this context many non-pharmacological complementary interventions have been developed whose effects continue to be evaluated to decide their importance in a multidisciplinary treatment of dementia. Therefore, in order to obtain this type of information, the primary caregiver is a key figure as they are the closest person to the living with dementia and will be heavily involved in all aspects of their care. Recent studies analysing the needs of caregivers and demonstrate the positive effects of an active programme of needs analysis and active support to the caregiver, in order to ease their physical and social burden [see Carbone, 2013].

The latest systematic reviews of studies on the identification of the factors responsible for the objective burden of non-professional caregivers reveals that there are about 39 predictors, mostly related to cognition, behaviour and daily functioning, directly or indirectly related to the caregiver's excessive burden [Thompson et al, 1998; Wolfs et al, 2012].

In this regard, it is essential to assess the needs of both people with dementia and their non-professional caregivers. Studies concerning this reveal that most of the unfulfilled needs can be found in the domains of memory, information, psychological distress and daily activities. Moreover, that people living with dementia report fewer (unfulfilled) needs than their caregivers [van der Roest et al, 2009].

The caregiver's burden is likely to be influenced by the behavioural and cognitive status of the person living with dementia, their attention span, stress, social isolation, the existing and premorbid relationship with the people living with dementia, availability of support resources, and the personal characteristics of the caregiver. Therefore, in order to reduce the burden and support the caregiver's health and well-being, it is necessary to evaluate and recognise the associated risk factors. The identification of these factors will lead to greater knowledge about them and the ability to manage them more successfully [Sansoni et al, 2013].

In this regard, interventions like those described in De Rotrou et al (2011) study, which demonstrate that active programmes devoted to the care of caregivers can have positive direct consequences, such as a better understanding of dementia as well as improving the capacity to cope with various problems resulting from dementia.

4.6 The application of information and communication technology (ICT) to support the care of the those living with chronic illness proves to be effective

Information and communication technology (ICT) or NICT (New Information and Communication Technologies) can be defined as those technologies that group elements and techniques used for the processing and transmission of information, mainly in the field of computers, internet and telecommunications. Therefore, any communicative element can be considered to be ICT provided it helps to manipulate, disseminate and share information through accessories or devices based on microelectronics, computers and telecommunications. All ICT tools basically have two characteristics: the first is that they have a very rapid evolutionary process; for example, some consider that the electric telegraph was the first ICT tool. The second feature is that they refer to a very broad concept which covers many elements. In this respect, technologies can be classified into three groups: networks, terminals and services. Within "networks" we can find landline telephone networks, television networks, broadband, mobile telephone networks, IP television and home networks. "Terminals" are physical devices and act as an access point for citizens to enter the information society; they are in a constant state of evolution and innovation. Examples of "terminals" are computers with their respective operating systems (Linux, Windows, Macintosh), internet browsers (computer software such as Mozilla Firefox, Google Chrome or Internet Explorer), mobile phones, televisions, portable audio players and or video game consoles. And finally, the term "services" refers to those supplier-customer models applied to the definition of ICT. These services vary depending on the technological resources and the progression of the way that a service is given. Examples of the most common services are: email, search engines, online banking, mobile services, e-commerce, etc. The most important thing is that thanks to information and communication technologies, mankind has undergone a radical change in the last century. The so-called "information age" owes its definition to the development of ICT and, through it, the human being can receive, acquire, store and process all kinds of information.

The European Union has been promoting the use of ICT in the context of neurodegenerative diseases with the aim to support their caregivers for many years now. Within this framework, they initially fostered and used ICT-based intelligent navigation and geolocation systems to improve the quality of life of vulnerable older people and their family caregivers. The main objective of all these initiatives has been to seek to improve the quality of life of older people and their family caregivers, due to the ease of use of ICT tools and their low cost implications [Magnusson et al, 2002].

In this context, the effectiveness of medical and social support through ICT to non-professional caregivers, regarding people living with chronic diseases, is essential in many ways. ICT based interventions have been proven effective and turn out to be positive for social support for most non-professional caregivers. Therefore, the identification and design

of appropriate ICTs for non-professional caregivers should continue and be supported in all their different contexts and tools such as the internet and social networks online support [Barrera-Ortiz et al, 2011; Lauriks et al, 2007].

ICT have been applied successfully under many viewpoints in assisting neurodegenerative diseases, being used as information measures and monitoring of associated changes in the development of dementia [Pilotto et al, 2011; Sacco et al, 2012; Romdhane et al, 2012; Van der Roest et al, 2010]. Their correct application has helped solve many everyday problems, creating a secure environment and facilitating joint decision-making (between family members, caregivers and people living with dementia) on the necessary assistance for people living with dementia [Olsson et al, 2012].

When non-professional caregivers of people living with dementia were provided with ICT healthcare tools based on social networks, it was suggested that their use has a positive impact both in improving the care and rehabilitation of the people living with dementia as well as helping with daily support and offering a diversity of solutions to address various daily problems associated with the illness. This shows that ICT systems can help, but they must be current (updated and well thought-out) and maintain the interest of the users involved [Lundberg, 2013]. In this regard, the analysis of different experiences based on the application of social networks specialising caregivers of people living with dementia, has revealed that their correct use is associated with better performance of the caregiver's responsibilities and helps to ease the associated burden, therefore affecting positively all aspects of the caregiver's health [Cheng et al, 2013]. At the same time, the quality of the information provided by the ICT helps to protect either against the risk of dementia or the dementia's progression [Amieva et al, 2010; Zunzunegui et al, 2003].

However, there are many factors that influence the use of ICT by caregivers and these must be taken into consideration when designing a tool of this kind. These characteristics can be summarised as: the caregiver's own knowledge about the illness and their familiarity with the health system regarding available support, their personal capacity and their own needs as a person and the social support received. Moreover, the confidence they have concerning the results of the assistance received, the perceived effort undertaken when using various technological support services and their ability to assume and manage the different roles of the people involved in caring are all factors which also play an important role [Chiu et al, 2011; Chiu et al, 2010; Dröes et al, 2005; Engström et al, 2009].

A recent systematic review on internet-based support interventions for caregivers of people living with dementia reveals that they can both improve the caregiver's welfare, as well as having positive consequences for the person being looked after. However, as the available supporting evidence lacks the necessary methodological quality, the future design of better clinical studies to emphasise their impact is essential [Boots et al, 2013].

Following this last suggestion, different solutions based on ICT platforms are currently being developed to support non-professional caregivers of people living with dementia, acting on clinical studies, such as the "Diapason" programme, based on the application of a compendium of psychoeducational interventions designed to prevent the caregiver's stress and ease their burden [Cristancho-Lacroix et al, 2013]. Its results indicate little acceptance of the program and high expectations from caregivers [Cristancho-Lacroix et al, 2015]. Another example is the internet intervention "Mastery over Dementia" based on a repository of videos intended to reduce psychological disorders, especially depressive symptoms in caregivers, whose results will appear in 2014 [Blom et al, 2013]. These projects follow in the footsteps of others which have already been evaluated, such as the DEM-DISC (DEMENTIA-specific Digital Interactive Social Chart), a web platform dedicated to address the service needs of caregivers, which demonstrated positive effects for both caregivers and people living with dementia [Van der Roest et al, 2010].

4.7 The need for evaluating the cost-effectiveness of interventions concerning the caregiver

According to recent studies, Alzheimer's disease is considered the most expensive neurodegenerative disease when comparing dedication time together with its associated costs, more than other diseases like Parkinson's ($17,492 annually for Alzheimer versus $3,284 generated by Parkinson's) [Costa et al, 2013]. This scenario makes it necessary to carry out further studies on the impact of intervention programmes for caregivers, as these account for the highest cost resulting from the disease [Health Quality Ontario, 2008]. It seems logical, therefore, that interventions to improve the welfare conditions of caregivers would have a direct impact on the costs associated with dementia care.

In this line, studies show that caregivers who are more able to adapt to the changes that characterise dementia feel more competent to care for the person and experience fewer psychological problems. This underlines the urgent need for more research on caregiver interventions that improves the adaptation of their role and that includes long-term monitoring and evaluating the cost-effectiveness of these interventions [de Vugt et al, 2013].

Other studies to assess the economic impact of other services provided for the PLWD, such as memory clinics and cognition-improving services, have not shown better results than programmes which support caregivers, thus demonstrating the success of opting for policies and support programmes which give direct assistance to the caregiver [Meeuwsen et al, 2013].

5 Justification

Dementia is a neurodegenerative condition with social, emotional and economical consequences. Interventions focused on treatment must be carried out in a multidisciplinary way in order to try and achieve the maximum possible number of positive effects concerning both protective factors and the lack of risk factors. Even so, in the absence of a cure, the goal should be to slow down its advance and to be able to ensure an acceptable quality of life of both the person living with dementia and their immediate circle as far as it is possible [Novella et al, 2012].

In recent years, professionals from around the world have concurred that the advancement of research should concentrate on an earlier diagnosis, on the reduction of the administration of neuroleptics and on increasing family support [Brooker et al, 2014; Lauritzen 2015].

In this sense, innovative European projects such as the "Alcove" (Alzheimer Cooperative Valuation in Europe, alcove-project.eu) aim to reduce pharmacological treatments for people living with dementia by focusing on and providing better family support.

Therefore, focus on ICT, as is the case of CAREGIVERSPRO-MMD in the present study [see section CAREGIVERSPRO-MMD platform description], use is necessary. ICT tools can achieve many of the objectives marked a priori by current health policies: access to effective and low-cost solutions, accessible repository of information, and the ability to integrate all kinds of tools and care strategies (geolocation, social networks, neurocognitive exercises, monitoring strategies...). This makes them ideal as support and assistance to the people living with dementia, to their caregivers and entire social and health ecosystem, even to foster applied research.

6 Research objectives

In 2006, the Médéric Alzheimer Foundation released the results of a study concerning memory centres and MRRC (Memory Resource and Research Centres) in France. This study revealed that 42 of the 136 centres which responded to the survey have provided a medical consulting service for caregivers (37 memory centres and 5 CMRR). The most common health problems which formed part of the consultation are listed in order of frequency in the following table:

Health-related queries of caregivers (% cases which reported each pattern)*	
Anguish, anxiety, depression, mental exhaustion	90%
Tiredness	48%
Sleep disorders	32%
Weight loss, eating disorders	23%
Cardiovascular diseases	23%
Memory loss	23%
Social isolation	18%
Joint pain	13%
Strong emotional reactions, nervousness, aggressiveness	8%
Decompensation of chronic illnesses	5%

* 40% of the relevant cases that responded to the survey

The main diagnoses evolved concerning depressive disorders, cardiovascular problems and eating disorders (anorexia nervosa, bulimia nervosa). In most cases, the follow-up consisted

of a change of doctor (either to another doctor and/or a specialist), but also in parallel with visits to a family association or psychologist.

With the publication of Eurofamcare in 2005 very different situations were reported from one country to another. The need was stressed for a systematic evaluation of the role and needs of caregivers. It also recommended the creation of psychological counselling for caregivers, discussion groups, and the organization of training to develop their knowledge of the dementia [Mestheneos et al, 2005] as well as the treatment of behavioural changes if necessary.

A review every 6 months of the caregiver burden was proposed by Etters et al (2008). This review is especially important to carry out when potentially dangerous situations can occur, such as the presence of behavioural changes, incontinence, physical dependence or conflict [Etters et al, 2008]

7 Hypothesis and Objectives

The dyad (formed by the person living with mild cognitive impairment (MCI) or mild to moderate dementia (PLWD) and their primary caregiver) and the social and health circle which is structured around it (family, friends, other dyads, health personnel, researchers), generates a lot of information regarding social and health concerns to improve living conditions and assessing the progression of the dyad. The existence of a platform based on Information and Communications Technology (ICT), capable of channelling all information generated and encouraging the search for solutions to specific problems, equipped with sensitive health monitoring tools and the possibility of putting all the different people living with mild cognitive impairment or dementia (mild to moderate) into direct contact; both the dyad as well as medical professionals or other dyads in the same situation; will improve the quality of care, control and monitoring of illness, resulting at the same time in a better diagnosis and an improvement in the subjective quality of life and health of its members.

7.1 Primary hypothesis

- The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the dyad, in the subjective quality of life of persons living with mild cognitive impairment or dementia (mild to moderate dementia) and in the level of burden experienced by the primary caregiver.

7.2 Secondary hypothesis

- The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the persons living with mild cognitive impairment or dementia (mild to moderate dementia), in their treatment adherence, behavioural and psychological symptoms and use of psychotropic drugs.

- The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the persons living with mild cognitive impairment or dementia (mild to moderate dementia), in their activities of daily living.

- The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the primary caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in psychological and neuropsychiatric disorders.

- The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the primary caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in perceived social support, success in relationships, self-esteem, purpose and optimism.

- The use during 18 months of CAREGIVERSPRO-MMD platform improves treatment adherence for the dyad (persons living with mild cognitive impairment or dementia (mild to moderate dementia) and their primary caregivers.

- The use during 18 months of CAREGIVERSPRO-MMD platform has a benefit for the dyad (persons living with mild cognitive impairment or dementia (mild to moderate dementia) and their primary caregivers), in the quality of the caregiving relationship.

- The use during 18 months of CAREGIVERSPRO-MMD platform reduces total costs of care (direct and indirect costs) for the dyad (persons living with mild cognitive impairment or dementia (mild to moderate dementia) and their primary caregivers.

- The use during 18 months of CAREGIVERSPRO-MMD platform reduces total number of hospitalisations for the persons living with mild cognitive impairment or dementia (mild to moderate dementia).

7.3 Primary objectives

Two primary objectives are considered:

- For persons living with mild cognitive impairment or dementia (mild to moderate dementia): to evaluate their subjective quality of life in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

- For primary caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia): to evaluate their perceived burden in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

7.4 Secondary objectives

7.4.1 Secondary objectives related to persons with MCI and PLWD

- To evaluate the activities of daily living for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the treatment adherence for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify an improvement from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the behavioural and psychological symptoms for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the neuropsychological functioning of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the total number of hospitalisations for persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

7.4.2 Secondary objectives related to primary caregivers

- To evaluate the subjective quality of life for caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the treatment adherence for caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify an improvement from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the behavioural and psychological health and wellbeing of caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

- To evaluate the perceived social support, success in relationships, self-esteem, purpose and optimism to caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months..

- To evaluate the use of psychotropic drugs for caregivers of persons living with mild cognitive impairment or dementia (mild to moderate dementia), in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

7.4.3 Secondary objectives related to dyad

- To evaluate the quality of caregiving relationship between caregiver and persons living with mild cognitive impairment or dementia (mild to moderate dementia) in dyads, in order to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

7.4.4 Secondary objectives related to economic and financial benefits

- To evaluate the direct and indirect costs of care to identify a benefit from use of the CAREGIVERSPRO-MMD platform during 18 months.

7.4.5 Secondary objectives related to CAREGIVERSPRO-MMD platform users

- To evaluate the degree of satisfaction of use of the CAREGIVERSPRO-MMD platform during 18 months.

8 Methods

8.1 Study design

This is a prospective, randomised, multicenter, controlled, parallel and longitudinal study. Measurements will be recorded at baseline (0) and at 3, 6, 9, 12, 15 and 18 months after and two groups will be compared: a group formed by dyads (people living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers) using the CAREGIVERSPRO-MMD platform and a control group formed by dyads without access to the platform.

8.1.1 Brief description of the CAREGIVERSPRO-MMD platform

The CAREGIVERSPRO-MMD platform focusing on people living with mild cognitive impairment or dementia (mild to moderate) and their caregivers, considering this "dyad" as the unit of care and offering both a variety of advanced, individually tailored services that will improve the quality of their lives and enable them to live well in the community for as long as possible.

Accessible through friendly and easy-to-use interfaces for mobile phones, tablets and web browsers, the services of the CAREGIVERSPRO-MMD platform includes social networking with other people living with dementia, caregivers and clinicians, clinical and psychological screening, personalised care plan and educational interventions tailored to each user's symptoms, medication reminder system and reporting to doctors and medical staff about treatment adherence level and other important clinical info.

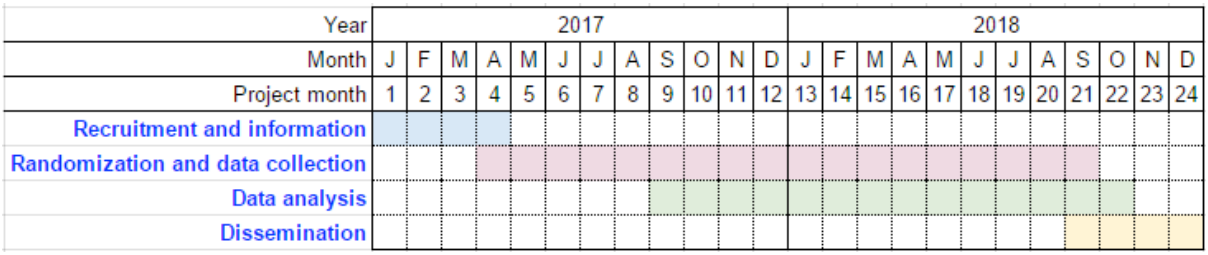
The CAREGIVERSPRO-MMD platform offers multiple benefits for its users, such as personalised care plans combining medication and behavioural treatments for both people living with mild cognitive impairment or dementia and their caregivers, reduction of stress and burnout phenomena of caregivers, discrete and constantly available monitoring of people living with mild cognitive impairment or dementia allowing fast adjustments to their care plan, efficient data collection of people living with mild cognitive impairment or dementia and caregivers by healthcare professionals, decision support for effective care plans and preventive interventions, as well as social networking.

[For more information: see section "Description CAREGIVERSPRO-MMD platform"]

8.1.2 Research calendar

- **Recruitment and information period** (4 months, from January 2017 to April 2017)
  - Starting information campaigns and strategies of the CAREVIGERSPRO-MMD study.
  - First project briefing session to inform caregivers and people living with mild cognitive impairment or dementia (mild to moderate) or their legal representatives who meet the criteria for inclusion and exclusion (screening).
  - Second project information session intended to provide additional information and detailed caregivers and people living with mild cognitive impairment or dementia (mild to moderate) or their legal representatives and stakeholders on the protocol and study characteristics. Signature of consent.
- **Randomization and data collection** (18 months, from April 2017 to September 2018)
  - Randomization of dyads at baseline and data collection through research visits at baseline, 6, 12, 18 months, and phone calls (economic data, treatment adherence, perceived social support, success in relationships, self-esteem, purpose and optimism) at 3, 9 and 15 months. Queries resolution.

    (for users of the platform a training session CAREGIVERSPRO-MMD platform will be performed).
- **Data analysis** (14 months, from September 2017 to October 2018)
  - Data management and pending queries.
  - Statistical analysis.
  - Statistical report and presentation of results.
  - Clinical report (October 2018).
- **Dissemination of study results** (4 months, from September 2018 to December 2018)
  - Development of scientific papers, multimedia slideshows and articles for the dissemination of project results.
  - Seminars, conferences and national and international scientific meetings on the theme of the project.



8.2 Inclusion / Exclusion / Study exit Criteria

8.2.1 Inclusion criteria

8.2.1.1 For persons living with mild cognitive impairment or dementia

- People, aged 50 and over, living in the community, who are able to give informed consent (or the legal tutor).

- Diagnosed with mild cognitive impairment (MCI) according to Petersen criteria [Albert et al, 2011] or mild to moderate dementia diagnosed according on DSM-IV criteria (Diagnostic and Statistical Manual, 4th edition) [American Psychiatric Association, 1994].

  [For more information: see sections "Core clinical criteria for the diagnosis of MCI" and "DSM-IV diagnostic criteria for dementia"]

- Having a Clinical Dementia Rating (CDR) of 0.5 for MCI, 1-2 for mild to moderate dementia.

- Having a Mini-Mental Exam score (MMSE) [Folstein, 1975] between 30 and 25 (inclusive) for MCI, and between 24 and 10 (inclusive) for dementia.

- Having a primary caregiver, familiar (or not), informal (or not) identified and also included in the study.

- Be willing to use Information Technology and Communications (ICT) according to the investigator criteria.

8.2.1.2 For primary caregivers

- People, aged 18 years and over, with no diagnosis or no evidence of mild cognitive impairment or mild to moderate dementia (according DSM-IV criteria) [American Psychiatric Association, 1994], who are able to give informed consent and with an intention to complete the study.

- Primary caregivers, informal (or not), familiar (or not), of person with mild cognitive Impairment or mild to moderate dementia.

- People with Internet access and basic knowledge and skills in managing internet and social networks, or keen to learn, according to the investigator criteria.

- Having a Geriatric Depression Scale (GDS-Yesavage - 15 items) score less than 11 at the time of entry into the trial indicating no severe depressive symptoms.

- Having no specific conditions (evaluated by the investigator) reducing their physical abilities below the norm for their age that would limit or impair CAREGIVERSPRO-MMD platform use.

- Be willing to use Information Technology and Communications (ICT) according to the investigator criteria.

8.2.2 Exclusion criteria

8.2.2.1 For people with mild cognitive impairment and people living with dementia

- Terminal or severe illness with survival prognosis less than 18 months.

- Having delusions, hallucinations, behavioural disturbances, that may interfere with the use of Information and Communications Technology (ICT) tools.

- Relevant sensory problems (visual or hearing impairment) or motor disability (such as paralysis of upper limb or disabling arthritis or disabling tremor, etc...) evaluated by the investigator that would interfere with the use of Information and Communications Technology (ICT) tools.

- Not speaking the language of the country where the pilot is being conducted.

8.2.2.2 For primary caregivers

- Terminal or severe illness with survival prognosis less than 18 months.

- Relevant sensory problems (visual or hearing impairment) or motor disability (such as paralysis of upper limb or disabling arthritis or disabling tremor, etc...) evaluated by the investigator that would interfere with the use of Information and Communications Technology (ICT) tools.

- Not speaking the language of the country where the pilot is being conducted.

8.2.3 Study exit criteria

- If the caregiver changes or if the caregiver can't continue his role of caregiver.

- Primary caregiver who do not use the platform during 2 months due to a justifiable reason according to the investigator criteria.

- Primary caregivers showing malicious or inappropriate CAREGIVERSPRO-MMD platform use according to the investigator criteria.

- Severe illness for the persons living with mild cognitive impairment or dementia (mild to moderate) or their caregivers evaluated by the investigator that interfere with the ability or potential to use Information and Communications Technology (ICT) tools.

- One member of the dyad want to retire informed consent and wants to withdraw from the study.

- Hospitalisation or institutionalisation >2 month of the people with mild cognitive impairment, people living with dementia or caregivers.

8.3 Recruitment and information

This phase will last for four months (From January 2017 to April 2017). In order to guarantee the inclusion of the sample in the study some strategies will be performed as follows:

- Verbal advertisement of study in local community settings and voluntary settings that provide support to people living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers.
- Organization of meetings, display posters, elaboration of hand-out information sheets.
- Advertising of the study at dementia awareness events.
- Online advertisement on local social media and dementia networks.
- Radio and media adverts and in newsletters by organisations supporting people living with dementia.
- Information campaigns and strategies developed by local medical partners to identify possible candidates for study sample.

Interested people will contact with investigators of the project who will plan a screening visit for evaluating inclusion/exclusion criteria and informing about characteristics of the study.

Step 1

During the initial contact authorized personnel (research assistants) from the pilot centre will propose to caregivers and their corresponding people living with mild cognitive impairment and dementia (mild to moderate), complying inclusion and exclusion criteria, to participate in the study. During this contact both MCI/PWLD and their caregivers will be given the information sheet for the study with details of study and the platform as well as verbal information about study. For those who express an interest in the research an appointment in order to enrol the components of the dyad at a time and place of their convenience.

Step 2

During the subsequent visit the investigator will offer detailed oral and written information about the study, explaining their characteristics, advantages, limitations, calendar, following-up and required contacts providing information sheet. Provide a chance to ask any questions. If after the session both MCI/PLWD and their caregiver agree with the explained conditions and protocol, show an understanding of it and comply with the inclusion and exclusion criteria, then they will be included in the study after the signing of informed consent.

8.4 Screening

In this phase inclusion and exclusion criteria will be checked for both patient living with mild cognitive impairment or dementia (mild to moderate) and their caregiver.

8.4.1 Sociodemographic variables

8.4.1.1 Sociodemographic variables for MCI and PLWD

Sociodemographic variables	**Values/Units**	**Visit**
Date of birth	(DD/MM/YY)	Screening
Gender	male/female	Screening
Socioeconomic status (SES) (only at baseline)	Upper, Upper middle, Lower middle, Upper lower, Lower (Kuppuswamy's socioeconomic scale [Sharma et al, 2012])	Screening
Education level	International Standard Classification of Education (ISCED-2011)	Screening
Relationship between care-recipient and caregiver	Father/mother, wife/husband/partner, son/daughter, daughter in law/son in law, sister/brother, other relative, neighbour, friend. (according to the RUD questionnaire)	Screening

8.4.1.2 Sociodemographic variables for primary caregivers

Sociodemographic variables	**Values/Units**	**Visit**

Date of birth	(DD/MM/YY)	Screening
Gender	male/female	Screening
Socioeconomic status (SES)	Upper, Upper middle, Lower middle, Upper lower, Lower (Kuppuswamy's socioeconomic scale [Sharma et al, 2012])	Screening
Education level	International Standard Classification of Education (ISCED-2011)	Screening
Professional occupation	International Standard Classification of Occupations (ISCO) - ISCO-88	Screening
Work status	Casual Appointment, Full Time, Indefinite Appointment, Part Time, Regular Appointment, Temporary Appointment, Term Appointment	Screening
Relationship between care-recipient and caregiver	Father/mother, wife/husband/partner, son/daughter, daughter in law/son in law, sister/brother, other relative, neighbour, friend. (according to the RUD questionnaire)	Screening

8.4.1.3 Comorbidities, medications and concomitant treatments for MCI/PLWD and caregivers

Information related to comorbidities and medications will be collected [for more information go to Data Management section].

That information will be codified following international dictionaries as World Health Organization's Drug Dictionary (WHO-DD), International Classification of Diseases (ICD-10) and WHO Adverse Reactions Terminology (WHOART) respectively.

8.4.2 Clinical variables for MCI and PLWD

CDR - Clinical Dementia Rating Scale

Created by: Morris, 1993

Purpose: The CDR is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member).

Administration time: 30-40 minutes

Submitted by: GP or medical specialist

Evaluated by: GP or medical specialist

Calculatation CDR score: https://www.alz.washington.edu/cdrnacc.html

Execution time: screening

Reference: Morris, J.C. The Clinical Dementia Rating (CDR): Current vision and scoring rules

Neurology, 1993; 43:2412-2414

MMSE - Mini-Mental State Examination

Created by: Folstein & Folstein, 1975

Purpose: To screen dementia, conceived as brief test for cognitive impairment. It includes questions about orientation, attention, recall and language.

Administration time: 20 minutes

Submitted by: Neuropsychologist, GP or medical specialist

Evaluated by: Neuropsychologist

Reference: Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-198.

8.4.3 Clinical variables for primary caregivers

GDS - Geriatric Depression Scale [short version]

Created by: Yesavage et al., 1982

Purpose: A Short Form consisting of 15 questions was developed in 1986. People who are physically ill and living with mild to moderate dementia, who have short attention spans and/or feel easily fatigued, find it more easy to use.

Administration time: 10 to 20 minutes

Submitted by: Caregiver

Evaluated by: Psychologist / GP/Medical specialist

Reference: Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49.

8.5 Description of randomization / stratification

Control group and intervention group will be randomly assigned. For each country a randomization list will be performed stratified by Mini Mental State Examination (MMSE). As the study aims to recruit same number of people with Mild Cognitive Impairment (MMSE 30-25), Mild Dementia (MMSE 24-20) and Moderate Dementia (MMSE: 19-10) a 33.3% in each level will be considered.

SAS PLAN procedure will be used to design the randomized design.

8.6 Intervention strategy

The platform studied, CAREGIVERSPRO-MMD is an online resource based on web technology accessible by computer, mobile and tablet, dedicated to provide both monitoring and assistance for people with mild cognitive impairment or people living with dementia. Its structure, as a social network, and its evaluation capacity with multiple questionnaires (dedicated to MCI/PLWD and their caregivers) allows them to share detailed information on the status and progress of the illness (cognitive status, medication usage, mood...). This personalisation leads users to access a range of information tailored to each situation, illness and assistance with the aim of improving the subjective quality of life of both the MCI/PLWD, carer and their immediate circle.

- 301 Dyads (50 followed by HUL, 100 by COO, 101 by FUB and 50 by CHU) formed by people living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers involved in the intervention group will target users of the online platform using all integrated resources.

- 301 Dyads (50 followed by HUL, 100 by COO, 101 by FUB and 50 by CHU) formed by people living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers involved in the control group without access to the online platform, but will be evaluated in all parameters relevant monitoring following the study protocol.

The intervention group will use a tablet (one for each member of the dyad, persons living with mild cognitive impairment or dementia (mild to moderate) and their primary caregiver) connected to the CAREGIVERSPRO-MMD platform and provided by the project staff. The tablet will have limited access to internet and the ability to be used for other applications other than those related to the activity of the CAREGIVERSPRO-MMD platform.

[For more information: see section "Description CAREGIVERSPRO-MMD platform" and "User Manual of the CAREGIVERSPRO-MMD platform"]

8.7 Measures to be collected

8.7.1 Physical variables for MCI/PLWD and primary caregivers

Physical variables	Values/Units	Visit
Weight	Kilograms (Kg) / grams (gr)	Baseline and every 6 months
Height	Meters (m) / centimeters (cm)	Baseline and every 6 months

8.7.2 Scales for primary outcomes

8.7.2.1 Scale for primary outcomes for MCI and PLWD

Subjective quality of life

ADRQL - Alzheimer's Disease Related Quality of Life

Created by: Rabins and Kasper, 1997.

Purpose: Is a 47-item scale that can be applied to people living with dementia. Five domains are studied: social interaction (12 items), awareness of self (8 items), enjoyment of activities (15 items), feelings and mood (5 items) and response to surroundings (7 items). It measures quality of life (QoL) in the last 2 weeks rated from 0 to 100 (good QoL).

Administration time: 10-15 minutes

Submitted by: Psychologists, GPs

Evaluated by: Psychologists, GPs

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Rabins P, Kasper et al. Measuring quality of life in dementia: conceptual and practical issues. Alzheimer Dis Assoc 1997; 11 (Suppl6): 100-4

8.7.2.2 Scale for primary outcomes for primary caregivers

Perceived burden

ZBI - Zarit Burden Interview

Created by: Zarit, Reever & Bach-Peterson, 1980

Purpose: To assess the level of burden experienced by the principal caregivers of older people living with dementia, through a 29-item scale. The revised version contains 22 items and is commonly used. Each item on the interview is a statement that the caregiver is asked to endorse using a 5-point scale (0=Never; 4 =Nearly Always).

Administration time: 5 to 10 minutes

Submitted by: Self-administered

Evaluated by: Psychologists, GPs

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Zarit, S.H., Reever, K.E. y Bach-Peterson, J. (1980). Relatives of the Impaired Elderly: Correlates of feelings and Burden. Gerontologist, 20, 649-655.

8.7.3 Scales for secondary outcomes

8.7.3.1 Scales for secondary outcomes for MCI and PLWD

Cognitive-Clinical symptoms

MMSE - Mini-Mental State Examination

Created by: Folstein & Folstein, 1975

Purpose: To screen dementia, conceived as brief test for cognitive impairment. It includes questions about orientation, attention, recall and language.

Administration time: 20 minutes

Submitted by: Neuropsychologist, GP or medical specialist

Evaluated by: Neuropsychologist

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-198.

Activities of daily living

IADL - Lawton Instrumental Activities of Daily Living Scale [8 items version]

Created by: Lawton & Brody, 1969

Purpose: Appropriate instrument to assess the ability to perform tasks necessary to live independently in the community. It takes into account 8 instrumental tasks (ability to use the telephone, shopping, food preparation, housekeeping, laundry, using transport, responsibility for own medications, ability to handle finances).

Administration time: 10 minutes

Submitted by: Caregivers (relatives, professional)

Evaluated by: Nurses / GPs, psychologists

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-186

BADL - Barthel ADL Index / Barthel Index of Activities of Daily Living

Created by: Mahoney & Barthel, 1965

Purpose: To measure performance in activity of daily living. It takes into account the level ability of 10 current tasks (bowel and bladder continence, grooming, toilet use, feeding, transfer, mobility, dressing, stairs, bathing). Possible total scores range from 0-20. Changes of more than 2 points reflect an improvement or impairment of functional status. Lower scores indicate increased difficulties.

Administration time: 10 minutes

Submitted by: Caregivers (relatives, professional), nurses

Evaluated by: Nurses / GPs, psychologists

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md Med J 1965; 14: 61-65

Behavioural-psychological symptoms

NPI - NeuroPsychiatric Inventory [12-item NPI]

Created by: Cummings, 1984

Purpose: To assess behavioural domains common in dementia. Contains 12 domains. These include: hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behaviour, sleep and night-time behaviour change, appetite and eating change.

Administration time: 0 to 30 minutes

Submitted by: Caregivers (relatives, professional)

Evaluated by: Psychologist / medical specialist

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Cummings, J., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology, 44, 2308-2314.

GDS - Geriatric Depression Scale [short version]

Created by: Yesavage et al., 1982

Purpose: A Short Form consisting of 15 questions was developed in 1986. People who are physically ill and living with mild to moderate dementia, who have short attention spans and/or feel easily fatigued, find it more easy to use.

Administration time: 10 to 20 minutes

Submitted by: MCI/PLWD or caregiver

Evaluated by: Psychologist / GP/Medical specialist

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49.

8.7.3.2 Scales for secondary outcomes for primary caregivers

Subjective quality of life

SF-36v2 - Medical Outcomes Study (MOS) 36-Item Short Form 2nd version

Created by: Ware jE, 1992

Purpose: The Optum™ SF-36v2® Health Survey asks 36 questions to measure functional health and well-being from the patient's point of view. It is a practical, reliable and valid measure of physical and mental health that can be completed in five to ten minutes. We refer to it as a generic health survey because it can be used across age (18 and older), disease, and treatment group, as opposed to a disease-specific health survey, which focuses on a particular condition or disease.

Administration time: 5-10 minutes

Submitted by: self-administered

Evaluated by: Psychologists, GPs

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-483.

Behavioural-psychological symptoms

GDS - Geriatric Depression Scale [short version]

Created by: Yesavage et al, 1982

Purpose: To evaluate depression in older people. It is a 30-item test; scores of 0-4 are considered average, depending on age, education, and complaints; 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression.

Administration time: 10 to 20 minutes

Submitted by: Caregivers (relatives, professional)

Evaluated by: Psychologist / GP/Medical specialist

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

Reference: Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982-1983;17(1):37-49.

STAI - State Trait Anxiety Inventory

Created by: Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983

Purpose: To measure trait and state anxiety. It can be used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes. It also is often used in research as an indicator of caregiver distress.

Administration time: 2 to 6 minutes

Submitted by: Self-administrated

Evaluated by: Psychologists, GPs

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

References: Elliott, T, Shewchuk, R, & Richards, J.S. (2001). Family caregiver problem solving abilities and adjustment during the initial year of the caregiving role. Journal of Counseling Psychology, 48, 223-232.

Shewchuk, R., Richards, J. S., & Elliott, T. (1998). Dynamic processes in health outcomes among caregivers of patients with spinal cord injuries. Health Psychology, 17, 125-129.

Spielberger, C. D. (1989). State-Trait Anxiety Inventory: Bibliography (2nd ed.). Palo Alto, CA: Consulting Psychologists Press.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.

Perceived Social Support

MSPSS - Multidimensional Scale of Perceived Social Support

Created by: Zimet, Dahlem, Zimet & Farley, 1988

Purposes: To assess an individual's perception of the social support he or she receives from family, friends and significant others; it is a 12-items self-report questionnaire.

Administration time: 5 minutes

Submitted by: Self-admistered

Evaluated by: Psychologist

Execution time: Baseline, 6, 12, 18 months

Data collection: The data will be collected during research visits

References: Marziali et al. (2006), Marziali et al. (2011) ; T. Anderson, L. Merkerson-Miller, D. Paniagua and M. Ivins-Lukse (2015)

Canty-Mitchell, J. & Zimet, G.D. (2000). Psychometric properties of the Multidimensional Scale of Perceived Social Support in urban adolescents. American Journal of Community Psychology, 28, 391-400.

Zimet, G.D., Powell, S.S., Farley, G.K., Werkman, S. & Berkoff, K.A. (1990). Psychometric characteristics of the Multidimensional Scale of Perceived Social Support Journal of Personality Assessment,55,610-17

Perceived success in relationships, self-esteem, purpose and optimism

FS - Flourishing Scale

Created by: Diener, 2009.

Purpose: The Flourishing Scale is a brief 8-item summary measure of the respondent's self-perceived success in important areas such as relationships, self-esteem, purpose and optimism. The scale provides a single psychological well-being score.

Administration time: 3-5 minutes

Submitted by: Self-administered

Evaluated by: Psychologists, GPs

Execution time: Baseline, 3, 6, 12, 15, 18 months

Data collection: The data will be collected during research visits (baseline, 6, 12 and 18 months) and by telephone calls made by the research personnel (3, 9 and 15 months)

References: Diener E, Wirtz D, Tov W, Kim-Prieto C, Choi D, Oishi S, Biswas-Diener R. (2009). New measures of well-being: Flourishing and positive and negative feelings. Social Indicators Research, 39, 247-266.

8.7.3.3 Scales for secondary outcomes for dyads

Social relationship between MCI/PLWD and their primary caregiver

DAS - Dyadic Adjustment Scale

Created by: Spanier GB, 1976

Purpose: To measure marital adjustment; unmarried or same-sex partners can also use it. Subjects rate the extent to which they and their partner agree or disagree on a range of issues and the frequency they engage in specific interactions, such as quarrelling.

Administration time: 5 to 10 minutes

Submitted by: Self-administered

Evaluated by: Psychologist / GP

Execution time: Baseline, 3, 6, 9, 12, 15, 18 months

Data collection: The data will be collected during research visits (baseline, 6, 12 and 18 months) and by telephone calls made by the research personnel (3, 9 and 15 months)

Reference: Spanier GB. Measuring Dyadic Adjustment: New Scales for Assessing the Quality of Marriage and Similar Dyads. Journal of Marriage and Family. 1976;38(1):15-28.

8.7.4 Medications, concomitant treatments, treatment adherence, comorbidities and adverse events

For people living with cognitive impairment or dementia (mild to moderate) and their primary caregivers, this information will be collected by doctors and codified following international dictionaries as World Health Organization's Drug Dictionary (WHO-DD), International Classification of Diseases (ICD-10) and WHO Adverse Reactions Terminology (WHOART) respectively.

Treatment adherence

Proportion of days covered (PDC)

Created by: Choudhry NK, et al.

Purpose: The PDC calculation is based on the fill dates and days supply for each fill of a prescription. The denominator for the PDC (at the patient-level) is the number of days between the first fill of the medication during the measurement period and the end of the measurement period. Then, the PDC is the proportion of days with available medication in the measurement period (follow up period). People living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers with a PDC ≥ 80% are considered as adherent and the proportions of adherents in both groups will be compared.

Submission schedule: Continuous

References: Choudhry NK, et al. Measuring Concurrent Adherence to Multiple Related Medications. Am J Managed Care. 2009;15:457-464.

Nau DP. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. Springfield, VA: Pharmacy Quality Alliance [Internet]. 2012

American Pharmacists Association (2013). Improving medication adherence in patients with severe mental illness. Pharmacy Today 19(6):69-80.

MMAS-8 - 8-item Morisky Medication Adherence Scale

Created by: Morisky et al. 2008

Purpose: The MMAS-8 was developed from a previously validated four-item scale and supplemented with additional items addressing the circumstances surrounding adherence behaviour. MMAS-8 scores can range from 0 to 8 and have been trichotomized previously into three levels of adherence, to facilitate use in clinical practice: high adherence: MMAS score, 8; medium adherence: MMAS score ≥6 to <8; low adherence: MMAS score <6.

Administration time: 3 minutes

Submitted by: self-administered, caregivers (relatives, professional)

Evaluated by: research personnel

Execution time: Baseline, 3, 6, 9, 12, 15, 18 months

Data collection: The data will be collected during research visits (baseline, 6, 12 and 18 months) and by telephone calls made by the research personnel (3, 9 and 15 months)

Reference: Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence measure for hypertension control. J Clin Hypertens 2008;10: 348–354.

8.7.5 Platforms Users

The user's satisfaction will also be assessed. Platform user's activity will be evaluated by means internal indicators.

C-MMD-USE - C-MMD User Satisfaction Scale

Created by: MobilesDynamics

Purpose: The questionnaire assessing satisfaction and expectations of the CAREGIVERSPRO-MMD platform users through short questions.

Administration time: 3-5 minutes

Submitted by: self-administered

Evaluated by: research personnel

Execution time: Baseline, 3, 6, 9, 12, 15, 18 months

Data collection: The data will be collected during research visits (baseline, 6, 12 and 18 months) and by telephone calls made by the research personnel (3, 9 and 15 months)

Internal indicators:

- Number of visits per time unit
- Average time of visits
- Visited sections and services used
- Activity on social networking platform
- Activity content platform

8.7.6 Economic variables

Resource Utilization

RUD - Resource Utilization in Dementia [version 4]

Created by: Wimo A, et al. 2012

Purpose: Is the most widely used instrument for resource use data collection in dementia, enabling comparison of costs of care across countries with differing health care provisions.

Administration time: 10 minutes

Submitted by: MCI/PLWD or caregivers (relatives, professional)

Evaluated by: research personnel

Execution time: Baseline, 3, 6, 9, 12, 15, 18.

Data collection: The data will be collected during research visits (baseline, 6, 12 and 18 months) and by telephone calls made by the research personnel (3, 9 and 15 months)

Reference: Wimo A, Gustavsson A, Jönsson L, Winblad B, Hsu MA, Gannon B. Application of Resource Utilization in Dementia (RUD) instrument in a global setting. Alzheimers Dement. 2013 Jul;9(4):429-435.e17. doi: 10.1016/j.jalz.2012.06.008. Epub 2012 Nov 9.

Perspective of Analysis

The economic study derivative of the CAREGIVERSPRO-MMD use should consider all costs and outcomes that are a consequence of the illness (cost of illness) or the health or social care interventions evaluated (economic evaluation). It will be evaluated the costs and outcomes to key health and social care providers or funders and to the people living with mild cognitive impairment or dementia (mild to moderate) and their families. These will include: the costs of hospital care, community-based health care services, social welfare services, and care provided by voluntary agencies or family and friends.

Measurement and Valuation of Costs

The economic study derivative of the CAREGIVERSPRO-MMD platform use, will describe and quantifies the resources used to produce health and social care and support for the people living with mild cognitive impairment or dementia (mild to moderate) and their caregivers.

The study will include costs of the CAREGIVERSPRO-MMD platform intervention, follow-up care and support for people living with mild cognitive impairment or dementia (mild to moderate) and their primary caregivers.

Total costs include: direct and indirect costs.

Direct costs. Medical and social care cost	
Concept	**Data collected**
Diagnostic procedures	Required
Nursing home care	RUD

Medications	Required
Added health costs	RUD
Laboratory costs	Required
Physician visits	RUD
Hospitalisations	RUD
Disease therapies	RUD
Adapting housing	Required
Residential or respite care costs	RUD
Social welfare services such as day centres	RUD

Direct costs. Non-medical care costs	
Concept	**Data collected**
Home health aides /telecare or telemedicine	Required
Respite care	RUD
Adult day services	RUD

Indirect costs	
Concept	**Data collected**
MCI/PLWD and caregiver lost productivity	RUD
Unpaid caregiving time	RUD
Care provided by family and friends	RUD
Care provided by voluntary agencies	RUD

8.8 Flowchart of data collection for the study

8.8.1 People with Mild Cognitive Impairment and People Living with Dementia

Pilot Study month		Screening	0	3	6	9	12	15	18
Measures to be collected	**Tool**								
Sociodemographic variables		*							
Physical variables			*		*		*		*
Comorbidity		*							
Adverse events									
Medication and concomitant treatments		*							
Treatment adherence	PDC								
	MMAS-8		*	+	*	+	*	+	*
Primary outcomes	**Tool**								
Subjective quality of life	ADRQL		*		*		*		*
Secondary outcomes	**Tool**								
Cognitive-Clinical symptoms	CDR	*							
	MMSE	*	*		*		*		*
Activities of daily living	IADL		*		*		*		*
	BADL		*		*		*		*
Behavioural-psychological symptoms	GDS		*		*		*		*
	NPI		*		*		*		*

8.8.2 Primary Caregivers

Pilot Study month		Screening	0	3	6	9	12	15	18
Measures to be collected	**Tool**								
Sociodemographic variables		*							
Physical variables			*		*		*		*
Comorbidity		*	.....	.....	.....	.....	.....	.....	.....
Adverse events			.....	.....	.....	.....	.....	.....	.....
Medication and concomitant treatments		*	.....	.....	.....	.....	.....	.....	.....
Treatment adherence	PDC		.....	.....	.....	.....	.....	.....	.....
	MMAS-8		*	+	*	+	*	+	*
Primary outcomes	**Tool**								
Cognitive-Clinical symptoms	ZBI		*		*		*		*
Secondary outcomes	**Tool**								
Subjective quality of life	SF-36v2		*		*		*		*
Behavioural-psychological symptoms	GDS	*	*		*		*		*
	STAI		*		*		*		*
Perceived social support	MSPSS		*	+	*	+	*	+	*
Perceived success in relationships...	FS		*	+	*	+	*	+	*

8.8.3 Dyads

Pilot Study month		Screening	0	3	6	9	12	15	18
Measures to be collected	**Tool**								
Caregiving relationship	DAS		*		*		*		*

8.8.4 Platform Users

Pilot Study month		Screening	0	3	6	9	12	15	18
Measures to be collected	**Tool**								
Satisfaction C-MDD					*		*		*

8.8.5 Economic variables

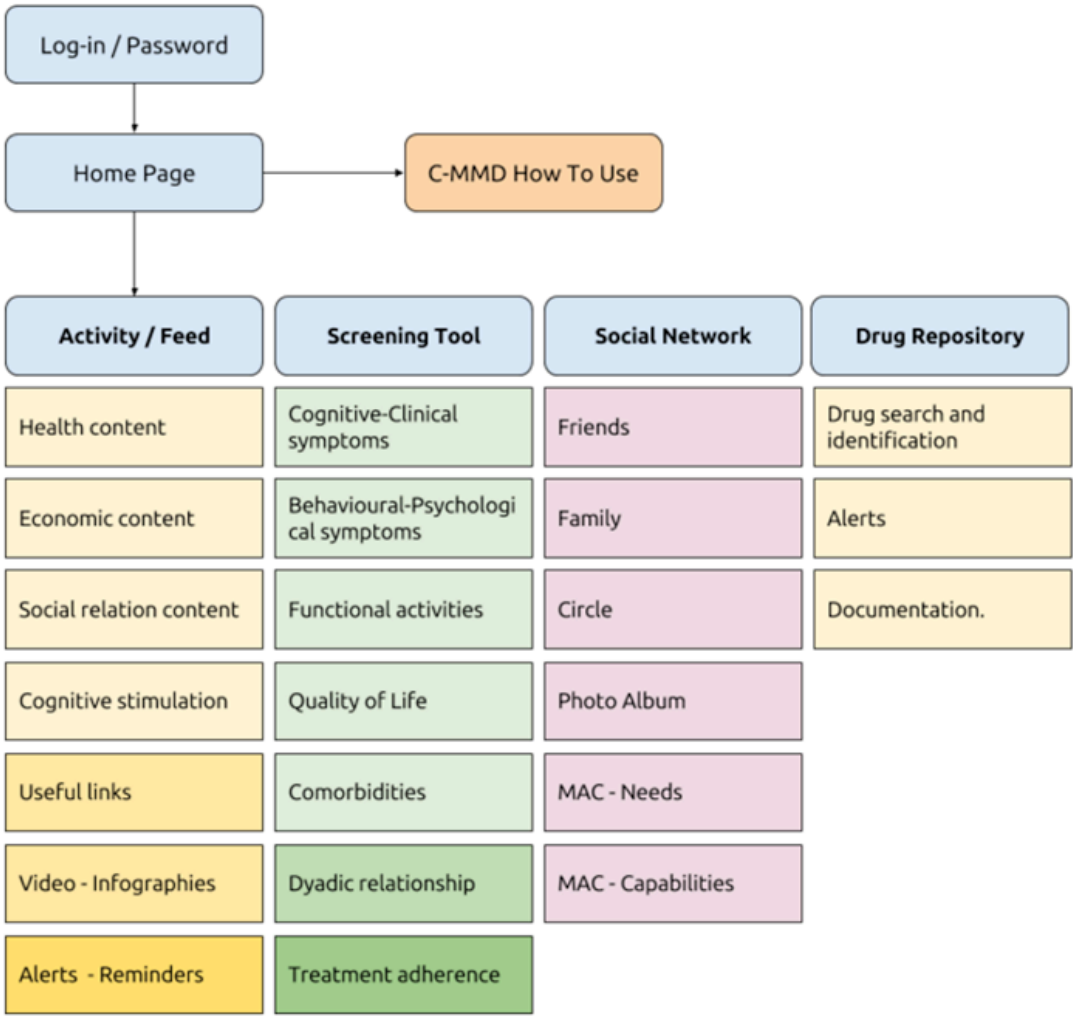
Pilot Study month		Screening	0	3	6	9	12	15	18
Measures to be collected	**Tool**								
Resource utilization	RUD		*	+	*	+	*	+	*
Direct and indirect costs			*	+	*	+	*	+	*

*	Clinical examination and data collection
+	Data collection by a telephone call
.....	Collected in a continuous way

9 CAREGIVERSPRO-MMD platform description

The CAREGIVERSPRO-MMD platform (C-MMD) is delivered in a free, password-protected, fully automated website, tablet and mobile application to be used by the caregivers, people living with dementia or with mild cognitive impairment, and health and social professionals. The C-MMD platform focuses on the dyad as unit of care. The main objective is to improve this unit of care experience and achieve greater efficiency and value from health and social delivery systems. C-MMD interventions are multicomponent and tailored.

9.1 C-MMD services for MCI/PLWD and their caregivers



9.2 Drug repository

The drug repository service does offer a range of functionalities. It is based on an innovative API (Application Programming Interface) architecture that covers 3 main domains: Drug search and identification, Alerts and Documentation

1) **Drug Search and identification**: Product name used to lookup branded or generic drugs.
2) **Alerts functions**: drug Allergy, interactions and warning modules
3) **Documentation functions and structured data**: Brand name, active ingredient(s), indications, route(s) of administration, contraindications, allergies, precautions, adverse effects, drug interactions, packaging information, „warnings (drug-food interactions, specific risks...), cautions for usage.

9.3 Social Network

The features will allow individuals to construct a public or semi-public profile within a bounded system, articulate a list of other users with whom they share a connection, and view and traverse their list of connections and those made by others within the system [Boyd, 2007]. Users can send friend requests via e-mail to other users. When a person receives a friend request, he may accept or decline it, or block the user altogether. If the user accepts another user as a friend, the two will be connected directly or in the “friend” degree. The user will then appear on the person's friend list and vice versa. Other degrees of relationship in the C-MMD platform is the “circle” (trusted connection) and “family” degree.

Another C-MMD Social Network service is the mutual assistance community where users’ needs are automatically matched with users resources. This service matches adequately users’ demands with user offers. Interface to identify users’ needs, interests (demands) and users’ abilities, knowledge, know-how, availability (offers). The system should be able to match and demands and services and permit users to meet each other's.

9.4 Screening Tool

The C-MMD screening focus on the following clinical domains for MCI/PLWD and their caregivers:

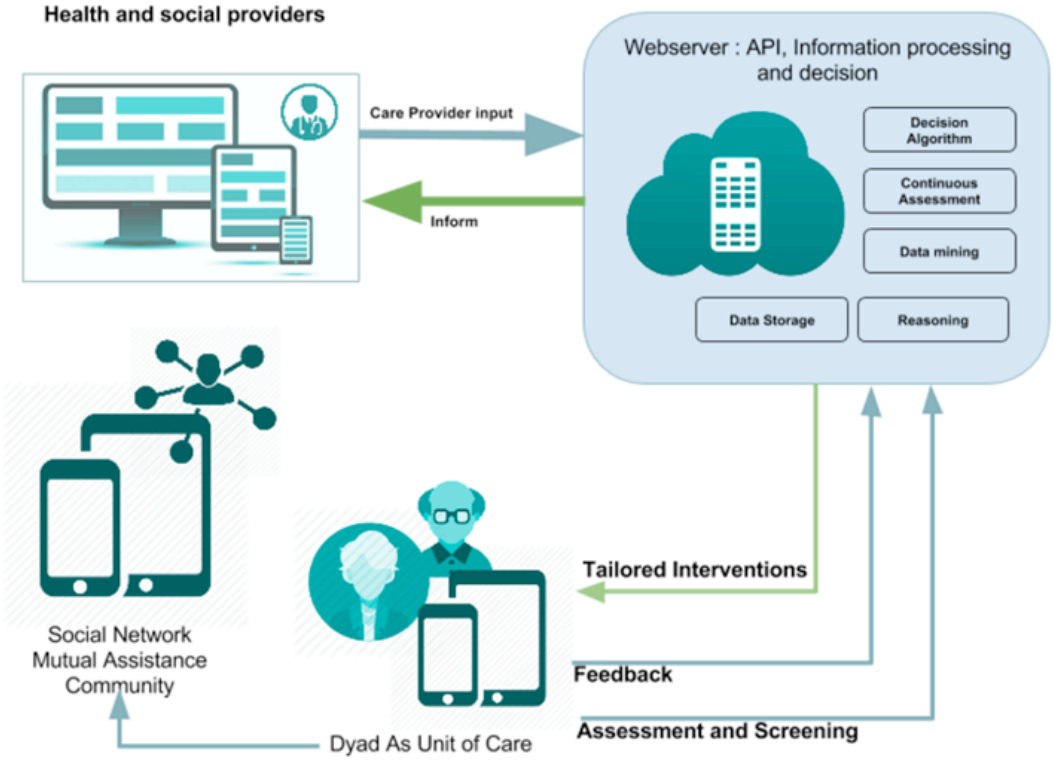
- Clinical and cognitive scales
- Psychological and behavioural scales

- Functional scales
- Quality of life
- Comorbidity
- Treatment adherence
- Dyad's relationship

9.5 Activity/feed

Based on the assessment result (screening tool), news, activities are proposed in form of tailored intervention to the user.

C-MMD provides tailored interventions to users (MCI/PLWD or caregiver). Tailored interventions are assessment-based programs: they deliver brief educational messages, address individual needs and are adapted to individual characteristics such as health conditions, culture, socioeconomic level, and educational level. For caregivers, the tailored interventions are based on cognitive theories of stress, a literature review, and the results of a study conducted by the C-MMD team. Interventions target the caregivers' beliefs, the caregivers' skills, and caregivers' social support and help-seeking behavior, and to meet and discuss with peers through social networks.



10 Data collection

10.1 Characteristics of data collection

Data will be introduced in a data management web page by research staff. That introduction will be made as follows:

1. At research visits baseline, 6, 12 and 18 months the whole information will be collected.
2. At telephone calls: 3, 9 and 15 months economic costs associated with care (scale RUD + other economic parameters), adherence to treatment (scale MMAS-8), perceived social support (MSPSS scale) and perceived success in relationships, self-esteem, purpose and optimism (FS scale) will be collected.

10.2 Description of the data management web page

The data management web page is intended to be a software platform in a secure web server for storing the clinical data generated during the screening and research sessions with pilot participants. The website will be accessed only by authorized users, under a secure environment on UPC servers (Universitat Politècnica de Catalunya - BarcelonaTech).

All the health related data generated during the pilot will be stored on the data management website, and the investigators will be able to analyze that data in real time in order to make regular checks on the whole process.

10.2.1 Data management

All data will be associated to a subject identified by its ID, and no relationship with real personal data will be stored on the server.

All the data included in point 8.7 of the pilot study protocol will be introduced on the server using different forms related with each particular subject, and can be reviewed by authorized users.

At the end of the pilot all information will be exported to standard formats in order to allow statistical researchers to perform the final analysis. More details can be found in Deliverable 7.3 “Data Management Plan”.

10.2.2 Roles

Three roles will be implemented on the pilot website, each of them representing a type of user with particular level of access to pilot data.

All user activity will be logged and monitored, and even a deletion action will be saved for the future. Each action of a user will be logged with a timestamp and a description of each action taken.

All users of the website must provide a valid email address and a double optin process will be performed in order to confirm each identity (user must confirm an email sent to the email address provided on a first step by clicking on a link with a personal, unique code).

A personal ID document will be required for each user in order to be sure all accesses are personal and audited.

10.2.2.1 Research assistants

All research assistants will be allowed to introduce data associated with subjects of the pilot. Filling in data from all pilot activity is the main function of this role.

All data from all research assistants will be accessible on the website, but researchers can be grouped in order to limit access to other pilot partners’ data if required.

10.2.2.2 Clinical research organization (CRO) user

CRO users will be able to review and access the information on a read-only mode in order to review all the researchers’ activities.

10.2.2.3 Technical administrator

Admin users will review all information is well maintained and will help other users on their tasks regarding the use of the website.

10.2.3 Security

Data management website will be hosted on UPC servers and will follow all security measures to ensure privacy and integrity of the data, with all activity audited on every moment. The databases are only accessible locally (i.e. only available to the C-MMD server itself) in order to prevent any unwanted connection from outside. The system and server configuration have been arranged in order to support local data encryption to avoid physical access to the hard disk drive. The server has a local firewall that only allows secure web connections to the Internet and verified IP addresses for development/updates of the C-MMD application. A local log file records every access to the server. The server is located in the UPC campus Data Center. This data center is a dedicated 250 m2 facility with controlled access, personal ID cards for authorized staff and video surveillance 24x7. The server has dedicated bandwidth and backup power system in order to guarantee availability. More details on security measures, reference to Deliverable 7.3 “Data Management Plan”.

11 Statistical Analysis

Two primary objectives are considered:

11.1 Primary objectives

These objectives are explained in the following:

- To evaluate the subjective quality of life of people living with mild cognitive impairment or dementia (mild to moderate), comparing the mean values at 18 months of the "Alzheimer's Disease Related Quality of Life" (ADRQL) scores between the control group and the intervention group (users of CAREGIVERSPRO-MMD platform).

- To evaluate the perceived burden by primary caregivers, comparing the mean values at 18 months of the "Zarit Burden Interview" (ZBI) scores between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

11.2 Secondary objectives

11.2.1 11.2.1 Secondary objectives related to persons with MCI or dementia

- To evaluate the activities of daily living comparing at 18 months, in people living with mild cognitive impairment or dementia (mild to moderate), scores of the "Lawton Instrumental Activities of Daily Living Scale" (AIDL) and "Barthel ADL Index" (BADL) between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate the treatment adherence in people living with mild cognitive impairment or dementia (mild to moderate) comparing at 18 months "Proportion of Days Covered" (PDC) between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform) and proportions of different levels of adherence according to "8-item Morisky Medication Adherence Scale" (MMAS-8).

- To evaluate the behavioural and psychological symptoms for persons living with mild cognitive impairment or dementia (mild to moderate dementia), comparing at 18 months the "Geriatric Depression Scale" (GDS) and "NeuroPsychiatric Inventory" (NPI) scores between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate the neuropsychological functioning in people living with mild cognitive impairment or dementia (mild to moderate), comparing at 18 months the "Mini Mental State Examination" test (MMSE) score between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate hospitalisations in people living with mild cognitive impairment or dementia (mild to moderate), comparing along the study the number of hospitalisations between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

11.2.2 Secondary objectives related to primary caregivers

- To evaluate the subjective quality of life related to health comparing at 18 month, in primary caregivers, both physical (PCS) and mental (MCS) component summary measures of SF-36v2 between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate the treatment adherence in primary caregivers, comparing at 18 months "Proportion of Days Covered" (PDC) between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform) and proportions of different levels of adherence according to "8-item Morisky Medication Adherence Scale" (MMAS-8).

- To evaluate the behavioural and psychological health and wellbeing comparing at 18 months, in primary caregivers, the "Geriatric Depression Scale" (GDS), The "State Trait Anxiety Inventory" (STAI) scores between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate the perceived social support comparing at 18 months, in primary caregivers, the "Multidimensional Scale of Perceived Social Support" (MSPSS) score

between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate the perceived success in relationships, self-esteem, purpose and optimism comparing at 18 months, in primary caregivers, the "Flourishing Scale" (FS) score between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- To evaluate the use of psychotropic drugs comparing at 18 months, in primary caregivers, proportions using them between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

11.2.3 Secondary objectives related to dyad

- To evaluate the quality of caregiving relationship between caregiver and people with MCI or PLWD comparing in dyads the values at 18 months of the "Dyadic Assessment Scale" (DAS) score between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

11.2.4 Secondary objectives related to economic and financial benefits

- Compare in caregivers the "Resource Utilization in Dementia" scale (RUD) score, direct and indirect costs, between the control group and the intervention group (users of the CAREGIVERSPRO-MMD platform).

- Economical parameters referred to costs not evaluated in RUD (diagnostic procedures, medications, laboratory, adapting housing, home health aides) will be also collected and compared between groups.

11.2.5 Secondary objectives related to CAREGIVERSPRO-MMD platform users

- A descriptive analysis from C-MMD User Satisfaction Scale.

11.3 Descriptive analysis

All variables will be described by using summary statistics as counts, mean, standard deviation, median, minimum, maximum and percentiles 25th and 75th for continuous variables and counts and percentages for categorical ones. 95% confidence intervals for the mean and free distribution confidence intervals for the median will be computed. Graphical analysis will be done as bar diagrams, scatter plots, box-plots, profiles and others.

11.4 Sample size

As there are two primary endpoints we will calculate two sample sizes and the bigger will be used. The resulting sample sizes are powering the two primary endpoints at European level considering the four countries pooled data.

For people living with mild cognitive impairment or dementia (mild to moderate) the objective is to demonstrate in users of the CAREGIVERSPRO-MMD platform a reduction of ≥10% in mean value of Alzheimer Disease Related Quality of Life total score (ADRQL) at 18 months.

The two-sided hypotheses are:

$$H_{01}: mP_{ADRQL} = mC_{ADRQL}$$

$$H_{11}: mP_{ADRQL} \neq mC_{ADRQL}$$

Where mP_{ADRQL} is the mean value of ADRQL at 18 months in the platform group and mC_{ADRQL} is the mean value of ADRQL at 18 months in the control group. A mean ADRQL value at 18 months in control group of 72 (percentage over the total score) and a mean ADRQL value of around 79 [Lyketsos et al, 2003] in the platform group are expected meaning an increase of around 10% in CAREGIVERSPRO-MMD platform users. Similar standard deviation of 15 is considered. Then, the question is to know how many people living with mild cognitive impairment or dementia (mild to moderate) will be needed to test a difference in mean values, if it exists, with a power of 0.9 at a two-sided significance level alpha equal to 0.05. Computation with SAS Proc glmpower is done to determine the sample size needed for testing in an analysis of covariance, with ADRQL at 18 months as dependent variable, ADRQL at baseline as covariate and group as independent variable. The calculated sample size reaches 230 people living with mild cognitive impairment or dementia (mild to moderate), 115 per group. The standard deviation used to calculate the sample size is adjusted to 15 due to the inclusion of the covariate and the actual power remains in 0.901. Considering a

dropout rate of 60% the sample size becomes 184 per group.

For primary caregivers the objective is to demonstrate in caregivers using the CAREGIVERSPRO-MMD platform a reduction of ≥20% in mean value of Zarit Burden Inventory (ZBI) at 18 months.

The two-sided hypotheses are:

$H_{02}: mP_{ZBI} = mC_{ZBI}$

$H_{12}: mP_{ZBI} \neq mC_{ZBI}$

Where mP_{ZBI} is the mean value of ZBI at 18 months in the platform group and mC_{ZBI} is the mean value of ZBI at 18 months in the control group. A mean ZBI value at 18 months in control group of 30 and a mean ZBI value of around 25.5 [Reed et al, 2014] in the platform group are expected meaning a decrease of around 15% in CAREGIVERSPRO-MMD platform users. Similar standard deviation of 15 is considered. Then, the question is to know how many primary caregivers will be needed to test a difference in mean values, if it exists, with a power of 0.9 at a two-sided significance level alpha equal to 0.05. Computation with SAS Proc glmpower is done to determine the sample size needed for testing in an analysis of covariance, with ZBI at 18 months as dependent variable, ZBI at baseline as covariate and group as independent variable. The calculated sample size reaches 430 primary caregivers, 215 per group. The standard deviation used to calculate the sample size is adjusted to 13 due to the inclusion of the covariate and the actual power remains in 0.900. Considering a dropout rate of 40% the sample size becomes 301 per group.

11.5 Primary analysis

Change in ADRQL/ZBI score defined as difference between 18 months value and baseline value will be compared between groups fitting an analysis of covariance with ADRQL/ZBI at 18 months as dependent variable, group as classification variable and baseline value as covariate. Confidence intervals for least square means will be computed.

11.6 Secondary analysis related to people living with MCI or dementia and their caregiver

Comparisons at 18 months of IADL score will be done fitting a polytomous logistic regression with group as independent variable.

Comparisons of treatment adherence will be done using proportions of MCI or PLWD/CG with PDC Covering ≥ 1 medication and covering the full regimen. Confidence intervals for the estimate of differences will be computed and a Chi-square test also applied for comparing proportions. MMAS-8 will be fitted with a two populations polytomous response for repeated measures.

Comparison of NPI (mild, moderate, severe) and GDS (normal, mild, moderate, severe) questionnaires at 18 months will be performed fitting a polytomous logistic regression with group as independent variable.

MMSE will be compared using proportion of people living with mild cognitive impairment or dementia (mild to moderate) who decrease their score and computing the confidence interval for the estimate of difference. A Chi-square test will also be done for comparing proportions.

Differences in SF-36v2 PCS and MCS component summary measures will be performed according to Quality Metric's Health Outcomes™ Scoring Software 5.0 available.

Comparisons between groups of the number of hospitalisations will be done computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. Same approach will be applied for STAI.

Comparisons of proportions of caregivers using psychotropic drugs between groups will be done computing the confidence interval for the estimate of difference. A Chi-square test will also be done for comparing proportions.

Comparisons at 18 months of MSPSS score and FS scale will be done computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. A rank analysis of covariance combined with Cochran-Mantel-Haenszel statistics will also be fitted to evaluate differences between groups.

When considering the scales over time, rate of change comparisons between groups of ZBI and ADRQL will be assessed fitting a random coefficient model incorporating random effects due to individual in both intercept and slope. IADL score and NPI questionnaire will be fitted with a two populations polytomous response for repeated measures. A rank analysis of covariance combined with Cochran-Mantel-Haenszel statistics will also be fitted to evaluate differences between groups for other non-centred scores.

Secondary analysis related to dyad

Comparisons at 18 months of DAS score will be done computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. A rank analysis of covariance combined with Cochran-Mantel-Haenszel statistics will also be fitted to evaluate differences between groups.

11.6.1 Secondary analysis related to economic and financial benefits

Overall efficiency savings to family and costs associated in both people living with mild cognitive impairment or dementia (mild to moderate) and their caregivers will be achieved by computing the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data. Overall efficiency savings will be performed in the same way.

Comparison of median time to institutionalisation will be computing by the confidence interval for the estimate of difference of median values using the Hodges-Lehmann approach for independent data.

Exploratory cost-effectiveness analysis of the platform related to caregivers will be performed computing incremental cost-effectiveness ratio (ICER) and incremental net benefit (INB). Variable of efficacy will be the reduction of ZBI at 18 months with respect to baseline. Policy decisions are made in each country and so country-specific results are important. However, country-specific analyses perhaps are based on fewer patients and will often fail to provide adequate precision for statistical analyses. To address these issues hypothesis test to evaluate homogeneity of results across countries, consider country effects or using shrinkage estimators can be applied. This will be taken in account depending of data. Results of costs will be converted to a common currency in order to be compared appropriately. As the time horizon is bigger than one year adjusting by discount rate will be applied.

12 Ethical Proceedings

12.1 Valid legal dispositions

All development of the study will be conducted according to the principles of the Declaration of Helsinki, Seoul, Korea revision (October 2008) for research involving human beings. Copies of the Declaration of Helsinki and subsequent amendments are provided under specific request or can be obtained through the website of the World Medical Association in http://www.wma.net/en/30publications/10policies/b3/.

The study will be executed according to the protocol that ensures compliance with rules of Good Clinical Practice (GCP), as described in the Harmonized Tripartite Guidelines for Good Clinical Practice ICH 1996.

According to international rules concerning realization of epidemiological studies and recorded in International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences-CIOMS-Geneve,1991), in the guidelines of the Order SAS/3470 / 2009 on post-authorization observational studies and the recommendations of the Spanish Society of Epidemiology (SEE) upon revision of the ethical aspects of epidemiological research, projects of such studies must, except in certain specific cases, undergo review by an independent committee. For this reason, the present study has been submitted for evaluation to an ethics committee and has to be notified and classified by the respective country Agency of Medicines and Health.

12.2 Benefit-risk evaluation for the subjects under investigation

During the study only data on regular clinical practice will be collected. The participant dyads in the intervention group will undergo no tests other than those under regular clinical practice for clinical management of dementia.

There are several risks that need to be managed:

1. For example, There is a possible psychological harm or distress because of inappropriate use of the platform (inappropriate language in post and comments/inappropriate posts)
2. Another risk concerns safe internet use. Participants from the control and the experimental groups will be able to use the tablets to connect to internet in general, not only to connect to the platform.
3. Participants distress: although we do not any expect participants to feel distress, it is possible that completing platform questions and reflecting on their own health and wellbeing might increase feelings of distress. Possible that for MCI/PLWD conducting memory assessments might be upsetting. Reading posts of others we hope will be

supportive and helpful but may be distressing. Will they be able to contact researchers? Be advised to contact their GP? List of local support organisations and meetings will be included on the platform? They will be inform prior to the focus group and the usability study that they are free to ask for a break at any point. In the event that a participant becomes distressed they will be referred to their health professional, like their general practitioner.

4. Time considerations: The tasks related to the platform might be time consuming for participants. However, they will be able to use the platform on their own pace and place, when they feel they have time.
5. Loss of ability to consent of the duration of the pilot.

12.3 Considerations on information to participants and informed consent

Participants will be given a Participant Information Sheet (PIS), and will be informed about the aims of the study, methodology and how are they will be required to use the platform, and confidentiality of data. Because the platform works as a social network, and because caregivers, health professionals, helpers etc. will have access to MCI/PLWD data, participants will need to be informed about this it. Then, participants will be asked to give their full consent to participate in the study by signing a consent form. Consent will be taken following the principles of the mental capacity act and in accordance with the procedures outlined by Warner, McCarney, Griffin, Hill & Fisher, 2008.

Participants should be informed of their right to withdraw at any time without giving a reason. Participants will also have the right to withdraw their data by a given time, prior to data analysis and writing up. In the case of written information about the study and informed consent of participation must be given by his/her legal representative. An example of PIS informed consent sheet for this study is provided in Supplements of this protocol.

12.4 Confidentiality of data and MCI/PLWD

Information regarding the identity of MCI/PLWD is considered confidential for all purposes. Identity of PLWD must not be revealed nor spread. Their data collected in the database during the study will be documented in a dissociated way linking it with a study code (MCI/PLWD code) so that only investigator may associate such data to identified or identifiable persons.

If by law or audit, it was mandatory the knowledge of the MCI/PLWD identity, the sponsor of the study for each pilot site should always maintain confidentiality rules. The database generated in the study will not contain any identification of the MCI/PLWD, only a numerical code from which is not possible to reveal his/her identity. This identity will be maintained

between the participants and researchers' relationships and will not be achieved without the consent of both.

Personal data (name, address, workplace of investigators) involved in the study will be stored electronically for the sole purpose of facilitating those logistical and organizational aspects required for the development of the study. The file is subject to confidential treatment under the provisions of the applicable law of the country.

Quotes from interviews: Participants will be informed in the information sheets that researchers might use direct quotes from their interviews for publication. However, these quotes will be anonymised, or will be presented under a different name.

12.5 Study recommendations and withholding of records

Investigators will be identified with a specific code. MCI/PLWD and their caregivers included will be coded with a correlative number assigned by the researcher behind the identification number of the investigator. Principal investigator of each centre will be in charge of keeping copies of the documentation of the study, the original signed informed consent and the records of participants' identities. Regarding how long data must be kept will depend on the country.

12.6 Responsibilities of study participants

12.6.1 Participant investigators

By signing the investigator commitment, participant investigators compromise agreed to efficiently and diligently carry out the study following this protocol according to generally accepted standards of good clinical practice and all standards and legal requirements related to realization of the study.

12.6.2 Obligations of members of the research team

- Ensuring all time for the welfare and safety of participants.
- Comply with the commitment to carry out the study according to the protocol as well as inform MCI/PLWD or their legal representatives about the aims of the study and obtain their informed consent.
- Keep the documentation at least 10 years after the final report of results.

- Aim to contribute to the dissemination of results in scientific articles and conferences.
- Be responsible for assuring that information collected and annotated in the database is accurate according to the information provided in this in the protocol.
- Know the origin of the collected data and associate them with participants' identification data, being responsible for not appearing in the database any information that could identify the participant (name, identification code, zip code, telephone...).
- All participating investigators will have to prepare and maintain a complete and accurate documentation of the study in compliance with standards of good clinical practice and national and local legal requirements and regulations. They will also have to register all data in the database for each participant within a reasonable period as required by this protocol.

12.6.3 Coordinator investigator

Coordinator investigator will have to comply with all obligations as participant and will also have to sign the final version of the protocol and any modification together with sponsor. He/she will be co-responsible of follow-up and final reports together with sponsor and diffusion of study results prior sponsor authorization.

12.6.4 Study monitor

Study monitor will have too to verify that information recorded in the database is reliable and consistent for which he/she will have to obtain collaboration of investigators participating in the study. Study monitor will follow the course of study and will inform doctors professionals about it. He/she will also notify any significant incidence damaging the course of the study of any issues arising during the pilot (slow patient enrolment, no complying of any inclusion/exclusion criteria, etc.).

12.6.5 Study sponsor

Study sponsor will be responsible for complying with current legislation. Also, if will have the following duties:

* Signing with coordinator investigator the protocol and any amendments of it providing investigators for eCRF and protocol submitting the protocol to the ethics committee or delegate this task to whom designate the sponsor presenting the study protocol and follow

up and final reports if required, provide a copy of the protocol and documents vouching for follow up procedures to entities supplying services to healthcare where the study will take place or delegate this task to whom designate the sponsor.

13 Dissemination of Results and Publication Policy

The CAREGIVERSPRO-MMD consortium have the following characteristics with respect to disseminating and applying their research findings:

Involve all partners in the dissemination of information about the partnership and project findings in forms that all partners can understand and use. This dissemination includes multiple audiences (e.g., community members, policy makers, local health professionals) and multiple formats (e.g., radio, newspapers, presentations at professional meetings, handbooks, policy position papers, scientific journal articles), with all partners involved as co-authors and co-presenters as their interests and circumstances allow.

- Development of scientific papers and posters for dissemination of results.
- Presentation in seminars, conferences and scientific meetings related to the topic.

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15 Supplements

15.1 User Manual of the CAREGIVERSPRO-MMD platform

15.1.1 Instructions for using the CAREGIVERPSRO system

The CAREGIVERPSRO system allows you to be part of a mutual assistance community. You can use the system through internet (www.caregivers.pro), with your mobile or with the tablets we will setup for you. There are a lot of functionalities within the system, so don't worry if you have the feeling it is too complex for you. You can have a positive experience using only some basic features and the system will help you to learn smoothly all the functionalities. In case of issue, you may send an email to support@caregivers.pro.

The tablet

We will set up the tablet for you. There is no need to switch it off. The system is ready for you to use. If the tablet isn't used for a while it will go to sleep. The screen may go blank, don't worry this is completely normal. Just touch the screen to re activate the machine. It may take 5-10 seconds to come back to life! If you can't get the tablet to come back to life check the machine is plugged in or charged. If it is plugged in, or charged, press the power button. The tablet will then set up automatically and CAREGIVERSPRO will appear again.

15.1.2 CAREGIVERSPRO overview

CAREGIVERSPRO is a digital platform based on social network where people with memory problem, formal and informal caregivers, health and social professionals can connect with other improving experiences of care. The mission is to support and develop a mutual assistance community to fight against dementia. People use CAREGIVERSPRO to create personal profiles, add other users as "friends" and share information related to dementia with them.

After signing up and adding friends, people communicate with some or all of their CAREGIVERSPRO friends by sending private, semi-private or public messages. Messages can take the form of a "status update" (a "post"), a private message, a comment about a friend's post or status, or a click of the "like" button to show support for a friend's update.

Once they learn CAREGIVERSPRO, most users will share all kinds of content - photos, videos, music, and more. They also join CAREGIVERSPRO interest groups related to dementia to communicate with people whom they might not otherwise know. After growing familiar with how CAREGIVERSPRO works, most people will also use special CAREGIVERSPRO applications that are available to plan events, play games like brain training and engage in other activities and cover:

- The need for general and personalized information;
- The need for support with regard to symptoms of dementia;
- The need for social contact and company and
- The need for health monitoring and perceived safety.

15.1.3 Learn CAREGIVERSPRO, Step-by-Step

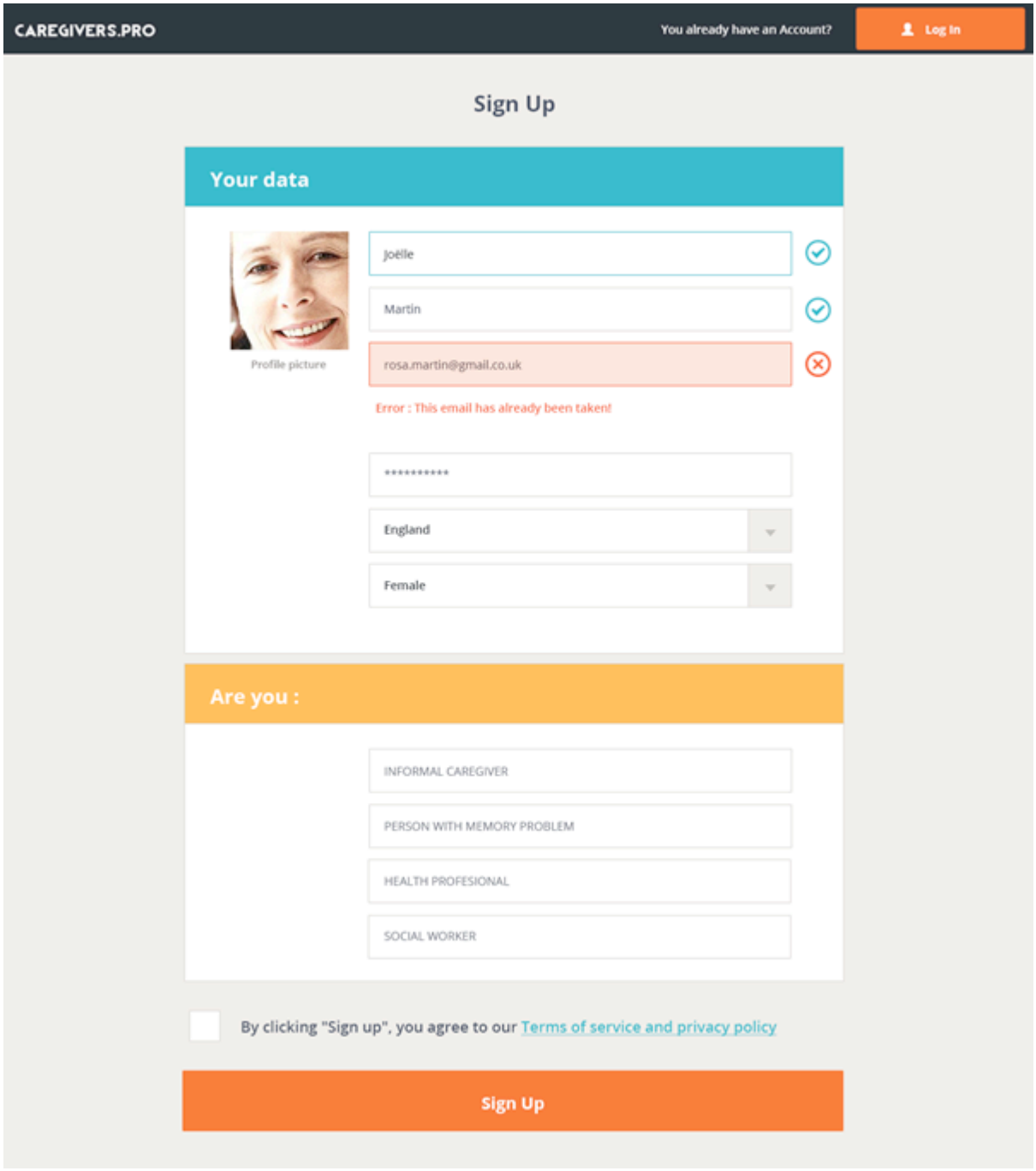
This part explains what every new CAREGIVERSPRO user should know to understand how CAREGIVERSPRO works in six areas listed below:

1. CAREGIVERSPRO Account Set-up
2. Using CAREGIVERSPRO Profile/Timeline
3. Connecting with Friends
4. Understanding CAREGIVERSPRO ‘s Interface
5. Communicating with Friends
6. Privacy Settings and Controls

15.1.3.1 CAREGIVERSPRO Account Set-up

The first step in using CAREGIVERSPRO is to sign up and get a new CAREGIVERSPRO account. Go to www.caregivers.pro and fill out the "Sign Up" form on. You should give your first and last name along with your email address and the rest of the form.

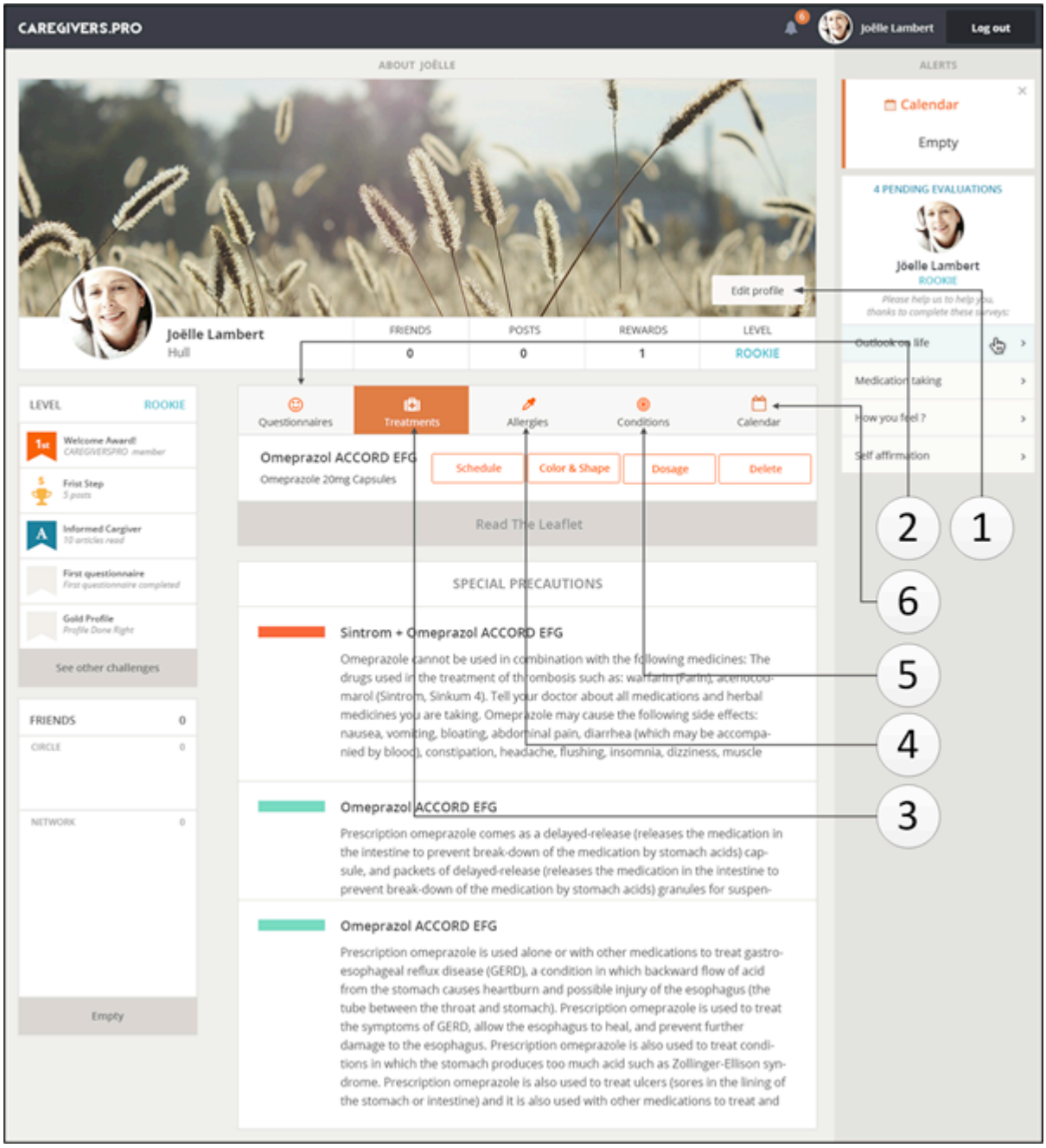
Click the orange "sign up" button at the bottom when you're done. CAREGIVERSPRO will send a message to the email address you provided with a link asking you to confirm your email address.



After signing up for CAREGIVERSPRO, you should fill out your CAREGIVERSPRO profile before you start connecting with many friends, so they'll have something to see when you send them a "friend request". Filing out your CAREGIVERSPRO profile consists on 6 steps:

- Step 1 - General information
- Step 2 - Questionnaires
- Step 3 - Treatments
- Step 4 - Allergies
- Step 5 - Conditions

- Step 6 - Events (“calendar”)



Step 1 - General information (“edit profile”)

To edit your basic personal info: go to your profile, Click “edit profile” at the bottom right of your cover photo. It concerns demographic background, interests and health information.

Demographic background: you can edit information like your first and last names, your spoken language, the city and country where you live, a short sentence that represents you (motto), your nationality, date of birth, and their gender.

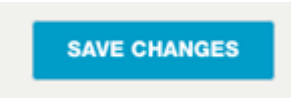
Interests: you will be able to select interests from a wide range, such as 'Making decisions about care' or 'Nutrition, appetite and weight'. This information will help us to provide tailored interventions.

Health information: They will also provide information about your conditions, such as your height and weight, conditions and other information that may have an impact on your treatment (e.g.: if you are driving).

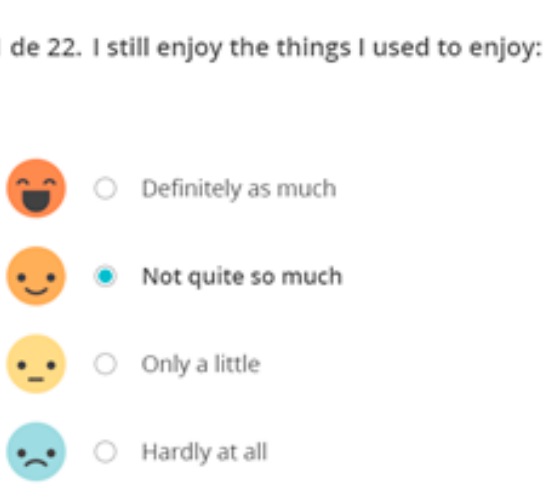
Privacy settings: You will be able to select who can see your information.

For example, you will be able to select who can send you a friend request, who can see your health outcome, or whom to share their treatments, posts, photos, avatar, followers, which people they follow, they friends/helpers, their date of birth, motto, email address, and telephone number with like showed in the figure on the right.	

Please don't forget to save all your changes by clicking the button "save changes" as shown on the right.

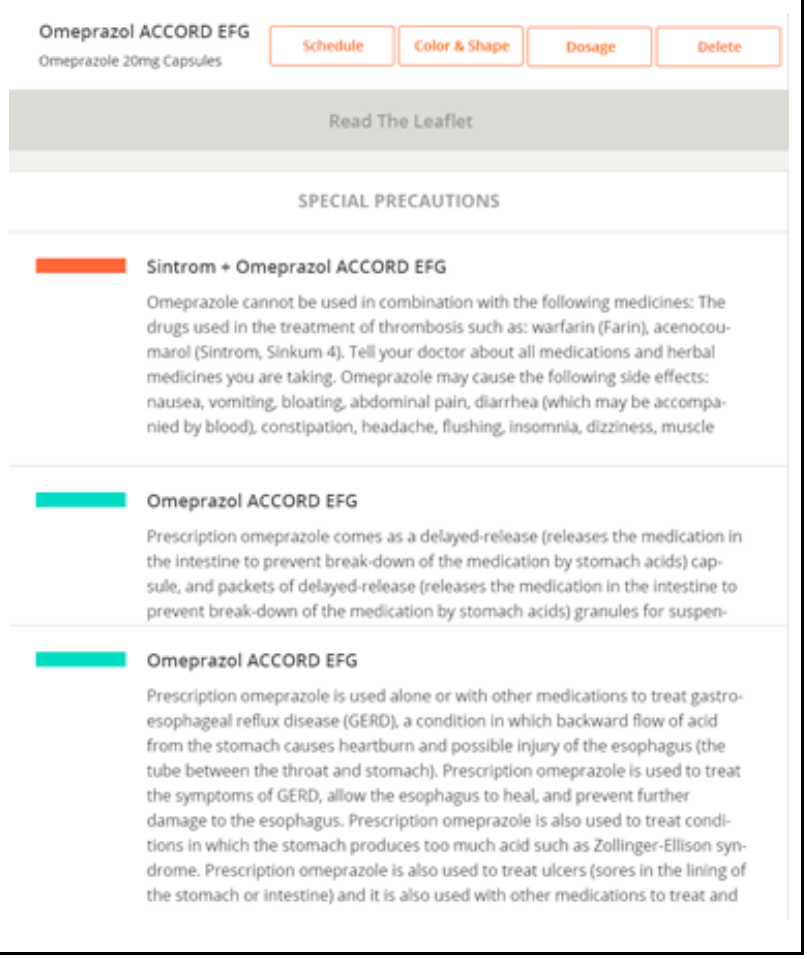


Step 2- Questionnaires

In order to provide the best content that fit your need, we will ask you to complete surveys from time to time. On the right, you have an example of a question from a questionnaire that will be proposed to you. Please help us to help you, thanks to complete these surveys.	

Step 3 - Treatments

In order to be able to send reminder, you can automatically populate CAREGIVERSPRO with your medication list no matter where you currently fill your prescriptions. No more tedious data entry or taking pictures of pill bottles, just **click search** and we'll do the rest. The app automatically keeps a log of the medications you've taken (and not taken), helping you track your progress over time. Never forget again!

The platform is linked to a drug repository that will permit you to have access to information about your treatment: - You can read the leaflet by clicking on “Rad the leaflet” - You will be informed about adverse effects with other drugs you are taking. - You will be informed about adverse effects with your conditions. - You will be informed about the treatment adverse effect. ***15.1.4***	

Step 4 - Allergies

You will select some allergies you have. This will help us to detect and inform you about potential drug adverse effects.

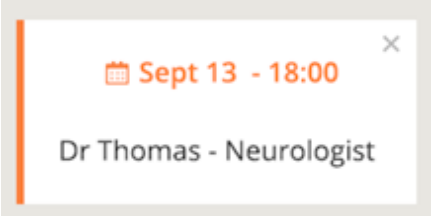
Step 5 - Conditions

This section is reserved to doctor and medical professional. For caregivers or person with memory problem, this section is an output section.

Step 6 - Events (“calendar”)

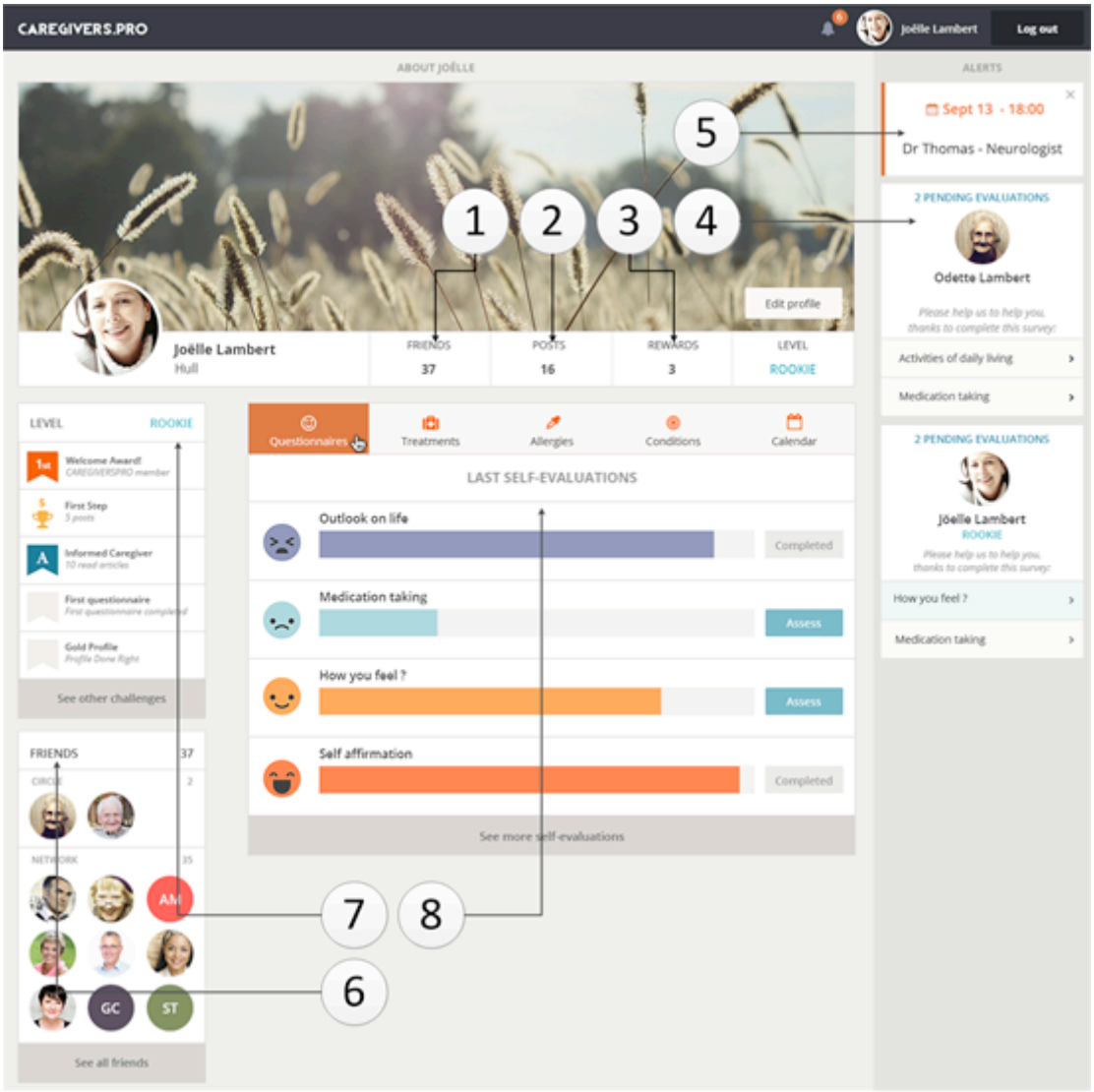
In this section, you can set up an event record that can be shared with your friends.

If you click on the “calendar” (Figure 1 – [6]), you can fill the following information: **Start date**, **end date**, **subject** and **privacy setting** (who can see this event)



After some times using CAREGIVERPSRO, you could have the same profile than Joelle:

1. Joelle is now in touch with in touch with friends and family
2. Joelle has made 16 posts (private messages, comments about a friend's post or status, or clicks of the "like" button to show support for a friend's update.)
3. Joelle won 3 badges, Joelle level is “ROOKIE”
4. Joelle added her grandmother (Odette) in her circle. As a dyad, they will share information and take care of each other. Joelle can complete Odette assessment, check Odette treatment adverse effect and share the result with health professional or within her circle.



5. Joelle has introduced one event. This event will be reminded and share with circle member.
6. Joelle has 37 friends. A “friends” may be part of the circle or the network. Circle members are the most trusted people. In a circle we can find caregivers, people with memory problems, supporting professionals and volunteers. Within a circle, we can share private, health information and create a basic community of care.
7. CAREGIVERSPRO is rewarding users and group of users (dyads and circle) for getting engaged with the community, participating in discussions with other users, watching videos, reviewing content, and other activities. In exchange for their participation, users, dyads and circles are awarded with badges and progress through levels of achievement. Joelle level is rookie.
8. Self-evaluation: from time to times, CAREGIRVERSPRO will ask Joelle to complete questionnaires. The result is displayed here. The survey also provides information

for the tailored intervention in the timeline. As Joelle is the primary caregiver of Odette, Joelle will also have to complete the Odette questionnaires.

15.1.4.1 CAREGIVERSPRO Timeline (news feed)

The CAREGIVERSPRO timeline (or feed) displays the stream of personalized status updates to each user of the social network on their home page, the tailored interventions based on questionnaires, the medication reminders, and the private and public messages.

User can personalize the content streams they see in order to have a better control over the CAREGIVERSPRO news feed, which is widely seen as a crucial component in the social network experience. CAREGIVERSPRO wants to provide the best-personalized newspaper related to dementia, for users.

15.2 Project Information Document for participants

Research institution: [enter text]

Address: [enter text]

Research coordinator name: [enter text]

Telephone: [enter text]

Email: [enter text]

Study Title: "*Multicentre pilot study to determine the benefits of CAREGIVERSPRO-MMD platform use based on the information and communications technology (ICT), dedicated to the support and assistance of dyads living with neurocognitive diseases including persons living with mild cognitive impairment or mild to moderate dementia and their primary caregivers*"

Mrs., Miss, Sir,

In the following we are presenting information about the study of CAREGIVERSPRO-MMD platform for which we would appreciate your voluntary participation.

Nineteen million people in Europe are affected by dementia with economic and social serious health consequences.

The inner circle of some people living with dementia is formed by the primary caregiver, friends and social and health services from the area with the aim to minimize the consequences of the illness.

Supporting a dependent person in the daily life is not trivial. Besides personal, professional and financial sacrifice that spouses and parents are offering to people living with dementia, there is an impact on the physical and moral health of caregivers and family.

Main goal of this work is to reduce the burden of caregivers and improve the quality of life of people living with dementia.

This study will last 18 months, it is run by a research staff of [enter text] that will provide you all necessary explanations about the study.

Study abstract:

According to the World Health Organisation [WHO, 2015] there are 46.8 million people living with some form of dementia worldwide for which there is currently no treatment or effective strategy that can halt or reverse their progressive cognitive impairment. As Europe's population is aging, and longevity is the main risk factor for developing dementia,

long-term care for older citizens will represent an increasing financial cost for society. There are currently 19 million people living with dementia in Europe, and this figure is expected to reach 31.5 million by 2050. To manage this transition, health policies of the EU and its member states are focused on enhancing elderly people's longevity and preventing their dependency. This has the double aim of increasing their subjective quality of life while reducing costs and increasing the effectiveness of healthcare. That is why the European project "CAREGIVERSPRO-MMD" (RIA, PHC-25-2015, PIC: 690211), with participating partners: the Universitat Politècnica de Catalunya (Spain), MobilesDynamics (Spain), University of Hull (United Kingdom), Q-Plan International LTD (Greece), COOSS Marche (Italy), Fundació Universitària del Bages (Spain), Rouen University Hospital (France) and the Centre for Research and Technology Hellas (Greece), aims at evaluating the web platform "CAREGIVERSPRO-MMD", accessible for computers, phones and tablets, and defined as an mHealth application specifically for caregivers and people living with mild cognitive impairment or mild to moderate dementia, which will provide value-added services based on social networks, tailored interventions, clinical strategies and gamification to improve the subjective quality of life of those living with cognitive impairment or dementia as well as that of their caregivers (dyads), thus supporting them to live in the community for as long as possible.

In order to evaluate the effectiveness and impact of the platform in people living with mild cognitive impairment or dementia (mild to moderate) together with their caregivers, a prospective, randomised, multicentre, controlled, parallel and longitudinal study was devised with 602 dyads (carried out in a multicentre study: 100 followed by HUL, 200 by COO, 202 by FUB and 100 by CHU), divided into two groups of equal numbers. The groups will be comprised of one "intervention" group with access to the platform and another "control" group without any access to it. During the following eighteen months, aspects related to the individuals' health (general health, neuropsychological functioning, activities of daily living, subjective quality of life, adherence to pharmacological treatment and comorbidities), social aspects (cohesion of the dyad, social support, success in relationships, self-esteem, purpose and optimism) and economic aspects (cost-effectiveness of the use of the platform) and the degree of satisfaction and usability of the platform by all users will be evaluated.

You are invited to participate in a research study being conducted by [enter text - insert name, position and School/Institute][enter if appropriate - under the Supervision of [Insert name, position, research center/Institute].]

How is the study being paid for?

The study is being sponsored by European Union's Horizon 2020 research and innovation programme under grant agreement No 690211. Project title: "*Self-management interventions and mutual assistance community services, helping people with dementia and caregivers connect with others for evaluation, support and inspiration to improve the care experience*".

What will I have to do?

Total study duration is 18 months. The study includes two groups: a “control” group and an "intervention" group. Each dyad (people living with dementia and their caregiver) will be randomly assigned to one of them.

People living with dementia and caregivers of "control" group will attend a full medical examination every 6 months (month 0, 6, 12, 18 of the study), and receive a phone call monitoring about care costs, adherence to treatment and well-being (month 3, 6 and 15 of the study).

People living with dementia and caregivers of "intervention" group actively will use the CAREGIVERSPRO-MMD platform after previous training. They will also attend a full medical examination every 6 months (month 0, 6, 12, 18 of the study) and answer a questionnaire of satisfaction in using the platform and receive a phone call monitoring on care costs, adherence to treatment and well-being (month 3, 6 and 15 of the study).

The intervention group will use a tablet (one for each member of the dyad, persons living with mild cognitive impairment or dementia (mild to moderate) and their primary caregiver) connected to the CAREGIVERSPRO-MMD platform and provided by the project staff. The tablet will have limited access to internet and applications other than those related to the activity of the CAREGIVERSPRO-MMD platform.

The CAREGEIVERSPRO-MMD platform provides users with updated information and personalized advice. Users can participate in discussion groups for sharing the same living situation and enjoy other experiences. They also may to know in any moment their treatments, have access to health specific evaluations and to dispose of a medical diary.

What benefits will I receive in participating?

Your participation will represent no cost for you. Immediate benefit in participating in the study is your contribution to knowledge and scientific development of direct application of technologies to the quality of life of caregivers and people living with dementia as demonstrated in other studies.

Will the study represent any discomfort or risk for me?

There is no risk nor discomfort from the use of CAREGIVERSPRO-MMD platform.

May I withdraw from the study?

Participation is entirely voluntary and you may abandon whenever you want with no explanation. This will not affect your relationship with the medical team.

May I spread my participation in the study

Yes, you can inform other people about the study providing you also inform people about medical team contact for further possible participation.

What if I require or need further information?

Please contact [enter text - INSERT names, positions and phone numbers – do not use private telephone numbers.]

What if I have a complaint?

This study has been approved by the [enter text] Ethics Committee. The Approval number is [enter approval number once the project has been approved]

If you have any complaints or doubts about the ethical conduct of this research, you may contact the [enter text] on Tel [enter text] or email [enter text]. All issues will be treated confidentially.

After a period of reflection, if you agree to participate in this study, you must complete and sign the "Informed Consent Form" for participation. You are given a copy of the full document. We remind you that participation is entirely voluntary and you may abandon whenever you want with no explanation.

Thanks for your cooperation.

You will receive more information about this study from the research team.

15.3 Informed consent form

15.3.1 15.3.1 Primary caregivers - People with mild cognitive impairment / People living with dementia

Informed Consent Form for:

Primary caregivers / People with mild cognitive impairment / People living with dementia / Legal representatives

Research "CAREGIVERSPRO-MMD"

"Pilot study multicenter the influence of CAREGIVERSPRO-MMD platform based on the information and communications technology (ICT), dedicated to the support and assistance of those affected by neurodegenerative diseases (people living with dementia and their primary caregivers) the quality of life, health and socioeconomic impact"

Promoting research: Universitat Politècnica de Catalunya – Barcelona Tech - European Union

Executing Research Center: XXX

Principal Investigator: XXX

The undersigned:_____

(Full name), being a person (or primary caregiver affected person from mild cognitive impairment or dementia living), have read and understand the information report on the study entitled "CAREGIVERSPRO-MMD" that has given me.

I have also had the opportunity to ask any questions that have seemed useful for understanding the study information getting clear answers and precise by Researcher / Doctor _____ who also explained to me the nature, objectives, expected benefits, the duration of the study and monitoring potential risks and limitations related to my participation in this research.

I'm absolutely clear that I am free to accept or reject my participation in this research.

I know it reserves the possibility that, by unilateral own decision, discontinue my participation in this research, at any time, without having to justify my decision. Naturally, this does not compromise the quality of future services at my disposal.

I received the assurance that they will make the best decisions necessary regarding the state of my health at all times, according to the current state of medical knowledge.

My consent doesn't release the investigator and the sponsor of the research of their responsibilities for preserving me all my personal rights protected by law.

I have read and I have been informed that this research project has been approved by the Research Ethics Committee Clinical XXX <date of acceptance> and the Agency XXX XXX (XXX). On the other hand: the local XXX responsible for research, management, insurance against liability for damage to the company XXX (contract number) that is at my disposal in the department / XXX XXX Research Centre.

I expressed my agreement that my medical records can be consulted linked to research under strict professional secrecy by staff. I agree that people who work in this investigation or have the mandate of the promoter and possibly a representative of the health authorities, have access to my information in the strictest confidence. I agree that data recorded during this investigation can be processed for analysis under the responsibility of the promoter. I have been aware that, in accordance with the law relating to data, files and freedoms X XXX XXXX, have the right to access and correct any information concerning my person. Also I have the right to make opposition to the transmission and dissemination of information covered by professional secrecy. Such rights I have committed to my doctor responsible in the context of this investigation and perfectly knows my identity.

The overall results of the research I communicate directly, if requested, in accordance with the Act of X XXX XXXX on the rights of patients and the quality of the health system.

I can at any time request additional information on the research project Researcher / Doctor _____
(Telephone number: _____), who proposed me personally to participate in this research.

After sufficient time to reflect before making my decision time, I freely and voluntarily agree to be involved in research CAREGIVERSPRO-MMD.

In XIX, XX XXX XXX Name of the participant in the research: Signature:	In XXX, XX XXX XXX Name of the person responsible for the research: Signature:

15.3.2 Legally responsible

Informed Consent Form for:

Legally responsible

Research "CAREGIVERSPRO-MMD"

"Pilot study multicentre the influence of CAREGIVERSPRO-MMD platform based on the information and communications technology (ICT), dedicated to the support and assistance of those affected by neurodegenerative diseases (people living with dementia and their primary caregivers) the quality of life, health and socioeconomic impact"

Promoting research: Universitat Politècnica de Catalunya – Barcelona Tech - European Union

Executing Research Center: XXX

Principal Investigator: XXX

The undersigned _____

(Full Name), as legal representative of the person_____(full Name)
I have read and understood the information leaflet on the study entitled CAREGIVERSPRO-MMD that has given me.

I have also had the opportunity to ask any questions that have seemed useful for understanding the study and have received clear answers and precise by Researcher / Doctor

_____

who also explained to me the nature, objectives, expected benefits, the duration of the study and monitoring, potential risks and limitations related to participation in this research in reference to the person who I represent.

I 'm absolutely clear that I am free to accept or reject on behalf of the person represented their participation.

I know it reserves the possibility that, by choice, the person I represent interrupt the participation in this research, at any time without having to justify my decision. Naturally, this will not compromise the quality of future services available to the person I represent.

I received the assurance that they will make the best decisions necessary at any time to benefit the health of the person who I represent, according to the current state of medical knowledge.

My consent doesn't relieve the investigator and the sponsor of the research of their responsibilities with regard to the person I represent to be retained all their rights under the law.

I have read and I have been informed that this research project has been approved by the Research Ethics Committee Clinical XXX <date of acceptance> and the entity / agency XXX XXX (XXX). On the other hand: the local XXX responsible for research, management, insurance against liability for damage to the company XXX (contract number) that is at my disposal in the department / XXX XXX Research Centre .

I expressed my agreement that my medical records can be consulted linked to research under strict professional secrecy by staff. I agree that people who work in this investigation or have the mandate of the promoter and possibly a representative of the health authorities, have access to my information in the strictest confidence. I agree that data recorded during this investigation can be processed for analysis under the responsibility of the promoter. I have been aware that, in accordance with the law relating to data, files and freedoms X XXX XXXX, have the right to access and correct any information concerning my person. Also I have the right to make opposition to the transmission and dissemination of information covered by professional secrecy. Such rights I have committed to my doctor responsible in the context of this investigation and perfectly knows my identity.

The overall results of the research I communicate directly, if requested, in accordance with the Law of X XXX XXXX on the rights of patients and the quality of the health system.

I can at any time request additional information on the research project Researcher / Doctor

_____

(Telephone number: _____), who proposed me personally to participate in this research.

Having had sufficient time to reflect before making my decision, I accept freely and voluntarily the person I represent is involved in the research CAREGIVERSPRO-MMD.

In XIX, XX XXX XXX	In XXX, XX XXX XXX
Name of the participant in the research:	Name of the person responsible for the research:
Signature:	Signature:

In XIX, XX XXX XXX Name of legal guardian of the participant in the research: Signature:	

15.4 CAREGIVERSPRO-MMD Promotional material


CAREGIVERSPRO-MMD
SERVICES
1 Social network services (C1-C2-C3-C4-C5 services)
2 Clinical, psychological and behavioural screening for caregivers and people living with dementia
3 Therapeutic education and educational intervention service
4 Medical information and treatment adherent service
5 Clinical and social report service
www.caregiverspromm-project.eu
Screening
Please complete the evaluations below:
Depressive episode
Burden Interview
CAREGIVERSPRO-MMD
CAREGIVERS
PEOPLE LIVING WITH DEMENTIA
C2 C3 C4
BOTH
PUBLIC SOCIAL NETWORK (i.e. Facebook)
C1
CLINICIANS & SOCIAL WORKERS
• Evaluation-oriented content service
• Clinical & social screening
• Medication information, treatment adherence service
• Gamification
• Clinical evaluation, reports, EHR
C5
EXPECTED
BENEFITS
People living with dementia
Personalised care plan, offering a combination of medication and behavioural treatments customised to their personal needs. A range of services for improving quality of life and independence, through the provision of solution focused information, support and advice through social networking and memory aids. Discrete, constantly available monitoring, allowing fast adjustments to the care plan.
Caregivers
Provision of social networking, information and wellbeing management tools to increase the social integration and support networks for caregivers. Personalised care plan, offering a combination of medication, behavioural and optimised treatment. Reduction of stress and burn-out phenomena.
Healthcare professionals
Reduction of time spent on administration, including data collection on people living with dementia and caregiver's wellbeing. Decision support for treatment options, correlations with behavioural changes and association with medical, psychological and social changes, allowing future improvement in care plans and preventive interventions.
Social worker professionals
Better understanding on elderly user evolution, behavioral changes and social participation. Intervention that facilitates monitoring, interaction and engagement in society.
Overall healthcare system
Reduced hospitalisations of people living with dementia and caregivers. Delayed need for people with dementia entering care homes.

16 Appendixes

1. Core clinical criteria for the diagnosis of MCI
2. DSM-IV diagnostic criteria for dementia
3. ADRQL - Alzheimer's Disease Related Quality of Life
4. BADL - Barthel ADL Index / Barthel Index of Activities of Daily Living
5. C-MMD-USE - CAREGIVERSPRO-MMD User Satisfaction Scale
6. CDR - Clinical Dementia Rating
7. DAS - Dyadic Adjustment Scale
8. FS - Flourishing Scale
9. GDS - Geriatric Depression Scale
10. IADL - Lawton Instrumental Activities of Daily Living Scale
11. KSS - Kuppuswamy's Socioeconomic Scale
12. MMSE - Mini-Mental State Examination
13. MMAS-8 - 8-item Morisky Medication Adherence Scale
14. MSPSS - Multidimensional Scale of Perceived Social Support
15. NPI - NeuroPsychiatric Inventory
16. RUD - Resource Utilization in Dementia
17. SF-36v2 - Medical Outcomes Study (MOS) 36-Item Short Form 2nd version
18. STAI - State Trait Anxiety Inventory
19. ZBI - Zarit Burden Interview

16.1 Core clinical criteria for the diagnosis of MCI

Reference:

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. 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. Alzheimers Dement. 2011 May;7(3):270-9. doi: 10.1016/j.jalz.2011.03.008. Epub 2011 Apr 21.

[link: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3312027/]

In this appendix, we outline the core clinical criteria for individuals with mild cognitive impairment (MCI). In considering the specifics of this clinical and cognitive syndrome, it is important to emphasize, as noted earlier in the text, that sharp demarcations between normal cognition and MCI and between MCI and dementia are difficult, and clinical judgment must be used to make these distinctions.

16.1.1 MCI - Criteria for the clinical and cognitive syndrome

16.1.1.1 Concern regarding a change in cognition

There should be evidence of concern about a change in cognition, in comparison with the person's previous level. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient.

16.1.1.2 Impairment in one or more cognitive domains

There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. If repeated assessments are available, then a decline in performance should be evident over time. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. An impairment in episodic memory (i.e., the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to a diagnosis of Alzheimer's disease (AD) dementia. (See the section on the cognitive characteristics later in the text for further details).

16.1.1.3 Preservation of independence in functional abilities

Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. It is recognized that the application of this criterion is challenging, as it requires knowledge about an individual's level of function at the current phase of their life. However, it is noteworthy that this type of information is also necessary for the determination of whether a person is demented.

16.1.1.4 Not demented

These cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning. It should be emphasized that the diagnosis of MCI requires evidence of intraindividual change. If an individual has only been evaluated once, change will need to be inferred from the history and/or evidence that cognitive performance is impaired beyond what would have been expected for that individual. Serial evaluations are of course optimal, but may not be feasible in a particular circumstance.

16.1.2 Cognitive characteristics of MCI

It is important to determine whether there is objective evidence of cognitive decline, and if so, the degree of this decline in the reports by the individual and/or an informant. Cognitive testing is optimal for objectively assessing the degree of cognitive impairment for an individual. Scores on cognitive tests for individuals with MCI are typically 1 to 1.5 standard deviations below the mean for their age and education matched peers on culturally appropriate normative data (i.e., for the impaired domain(s), when available). It is emphasized that these ranges are guidelines and not cut-off scores.

16.1.2.1 Cognitive assessment

As noted earlier in the text, impairment in episodic memory (i.e., the ability to learn and retain new information) is most commonly seen in MCI patients who subsequently progress to a diagnosis of AD dementia. Research studies have shown that there are a variety of episodic memory tests that are useful for identifying those MCI patients who have a high likelihood of progressing to AD dementia within a few years. These tests share the characteristic that they assess both immediate and delayed recall, so that it is possible to determine retention over a delay. Many, although not all, of the tests that have proven

useful in this regard are word-list learning tests with multiple trials. Such tests reveal the rate of learning over time, as well as the maximum amount acquired over the course of the learning trials. They are also useful for demonstrating that the individual is, in fact, paying attention to the task on immediate recall, which then can be used as a baseline to assess the relative amount of material retained on delayed recall. Examples of such tests include (but are not limited to): the Free and Cued Selective Reminding Test, the Rey Auditory Verbal Learning Test, and the California Verbal Learning Test. Other episodic memory measures include: immediate and delayed recall of a paragraph such as the Logical Memory I and II of the Wechsler Memory Scale Revised (or other versions) and immediate and delayed recall of nonverbal materials, such as the Visual Reproduction subtests of the Wechsler Memory Scale-Revised I and II.

Because other cognitive domains can be impaired among individuals with MCI, it is important to examine domains in addition to memory. These include: executive functions (e.g., set-shifting, reasoning, problem-solving, planning), language (e.g., naming, fluency, expressive speech, and comprehension), visuospatial skills, and attentional control (e.g., simple and divided attention). Many validated clinical neuropsychological measures are available to assess these cognitive domains, including (but not limited to): the Trail Making Test (executive function), the Boston Naming Test, letter and category fluency (language), figure copying (spatial skills), and digit span forward (attention).

If formal cognitive testing is not feasible, then cognitive function can be assessed using a variety of simple, informal techniques. For example, the clinician can ask a patient to learn a street address and to recall it after a delay interval of a few minutes (e.g., John Brown, 42 Market Street, Chicago). Alternatively, the clinician can ask the patient to name three objects (e.g., a pen, a paper clip, and a dollar bill), place them in different locations around the room and subsequently ask the patient to recall the names of the objects and their locations, again after a brief delay. These types of approaches are relatively easy to perform during an office visit, and will yield informative results. It is important, however, for clinicians to recognize that these informal tests will likely be insensitive to subtle cognitive dysfunction during the early stages of MCI, and will often yield normal performance. In addition, these approaches typically do not assess cognitive domains beyond memory.

Finally, it must be recognized that atypical clinical presentations of AD may arise, such as the visual variant of AD (involving posterior cortical atrophy) or the language variant (sometimes called logopenic aphasia), and these clinical profiles are also consistent with MCI due to AD.

16.1.2.2 Summary of clinical and cognitive evaluation

The initiation of a clinical and cognitive evaluation typically includes a cognitive concern expressed by the patient, an informant, or a clinician observing the patient's performance.

Cognitive decline can be documented by means of the history from the patient, preferably corroborated by an informant, or on the basis of observation by the clinician. Ideally, if serial assessments are available, they would be preferable, but in the setting of a single evaluation, this information is inferred from the history. The patient's cognition is assessed and found to be outside the normal range of function for the patient's age and educational background, but not sufficiently impaired to constitute dementia. The impairment can involve one or more cognitive domains. The clinician determines whether memory is prominently impaired, or whether the impairments in other cognitive domains predominate, such as spatial or language impairment. Typically, memory is the most common domain involved among patients who subsequently progress to AD dementia, as noted earlier in the text. There is generally mild functional impairment for complex tasks, but basic activities of daily living should be preserved, and the person should not meet criteria for dementia. It should be noted that the clinical syndrome, as summarized in this section and Table 1, is almost identical to the one previously described by Petersen et al [Petersen et al, 1999; Petersen et al, 2004; Winblad et al, 2004].

Table 1. Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
- Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities
- Not demented

Examine aetiology of MCI consistent with AD pathophysiological process

- Rule out vascular, traumatic, medical causes of cognitive decline, where possible
- Provide evidence of longitudinal decline in cognition, when feasible
- Report history consistent with AD genetic factors, where relevant

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Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

16.1.2.3 Longitudinal cognitive evaluation

Evidence of progressive decline in cognition provides additional evidence that the individual has "MCI due to AD," as noted earlier in the text. Thus, it is important to obtain longitudinal assessments of cognition, whenever possible. It is recognized that a diagnosis will likely need to be given without the benefit of this information; however, obtaining objective evidence of

progressive declines in cognition over time is important for establishing the accuracy of the diagnosis, as well as for assessing any potential treatment response.

16.1.2.4 Cautionary issues pertaining to cognitive assessment

It is important to emphasize that virtually all cognitive tests are sensitive to differences in age, education (i.e., literacy), and/or cultural variation among individuals. Age and educational norms are available for some tests, but few have norms that pertain to the oldest old (individuals aged ≥90 years). Moreover, considerable work remains to establish the reliability of cognitive tests across populations with wide cultural variation.

16.1.3 Aetiology of the MCI clinical and cognitive syndrome consistent with AD

Once it has been determined that the clinical and cognitive syndrome of the individual is consistent with that associated with AD, but that the individual is not demented, the clinician must determine the likely primary cause, for example, degenerative, vascular, depressive, traumatic, medical comorbidities, or mixed disease. Typically, this information is derived from further historical information and ancillary testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment) that may prove informative.

To meet the core clinical criteria for MCI, it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition (e.g., vascular, traumatic, medical). The goal of such an evaluation is to increase the likelihood that the underlying disease is a neurodegenerative disorder with characteristics consistent with AD. This diagnostic strategy is similar to the one that is used to diagnose “dementia due to AD.” This may include seeking evidence for:

(1) Parkinsonism, including prominent visual hallucinations, and rapid eye movement sleep abnormalities, often seen in dementia with Lewy bodies,

(2) multiple vascular risk factors and/or the presence of extensive cerebrovascular disease on structural brain images, which is suggestive of vascular cognitive impairment,

(3) prominent behavioural or language disorders early in the course of disease that may reflect frontotemporal lobar degeneration, or

(4) very rapid cognitive decline that occurs over weeks or months, typically indicative of prion disease, neoplasm, or metabolic disorders. It should be noted that the pathological features of some of these disorders can exist in combination with AD (e.g., Lewy bodies and vascular disease), particularly among individuals at an advanced age.

The presence of vascular pathology, in the setting of MCI, is particularly challenging from a diagnostic perspective. Because AD pathology frequently coexists with vascular pathology, particularly at older ages, both may contribute to cognitive dysfunction. Thus, during life, it may be difficult to determine which pathological feature is the primary cause of the cognitive impairment.

Among the oldest old (i.e., those aged ≥90 years), there are additional difficulties in determining the aetiology of the cognitive decline. For example, the pathological criteria for AD remain unclear for the oldest old.

16.1.3.1 Role of autosomal genetic mutations for AD

An additional issue is the role of genetics in the diagnosis. If an autosomal dominant form of AD is known to be present (i.e., mutation in APP, PS1, PS2), then the development of MCI is most likely the prodrome to AD dementia. The large majority of these cases develop early onset AD (i.e., onset below 65 years of age). There remains, however, variable certainty about the time course over which the progression from MCI to AD dementia will evolve in these individuals [Schellenberg et al, 2006].

16.1.3.2 Role of genes that increase risk for AD

In addition, there are genetic influences on the development of late onset AD dementia. To date, the presence of one or two ε 4 alleles in the apolipoprotein E (APOE) gene is the only genetic variant broadly accepted as increasing risk for late-onset AD dementia, whereas the ε2 allele decreases risk. Evidence suggests that an individual who meets the clinical, cognitive, and etiologic criteria for MCI, and is also APOE ε4 positive, is more likely to progress to AD dementia within a few years than an individual without this genetic characteristic. It has been hypothesized that many additional genes play an important, but smaller role than APOE; these additional genes will also confer changes in risk for progression to AD dementia [Bertram et al, 2010].

16.1.4 References

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- Petersen RC. Mild cognitive impairment. J Int Med. 2004;256:183–94
- Petersen RC, Smith G, Waring S, Ivnik R, Tangalos E, Kokmen E, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56:303–8

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- Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Nordberg A, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256:240–6

16.2 DSM-IV diagnostic criteria for dementia

Reference:

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington, D.C.: American Psychiatric Press, 1994.

The disorders in the "Dementia" section are characterized by the development of multiple cognitive deficits (including memory impairment) that are due to the direct physiological effects of a general medical condition, to the persisting effects of a substance, or to multiple aetiologies (e.g., the combined effects of cerebrovascular disease and Alzheimer's disease). The disorders in this section share a common symptom presentation but are differentiated based on aetiology. The diagnostic features listed in the next section pertain to Dementia of the Alzheimer's Type, Vascular Dementia, Dementia Due to HIV Disease, Dementia Due to Head Trauma, Dementia Due to Parkinson's Disease, Dementia Due to Huntingdon's Disease, Dementia Due to Pick's Disease, Dementia Due to Creutzfeldt-Jakob Disease, Dementia Due to Other General Medical Conditions, Substance-Induced Persisting Dementia, and Dementia Due to Multiple Aetiologies. In addition, Dementia Not Otherwise Specified is included in this section for presentations in which the clinician is unable to determine a specific aetiology for the multiple cognitive deficits.

16.2.1 Diagnostic Features

The essential feature of a dementia is the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning. A diagnosis of a dementia should not be made if the cognitive deficits occur exclusively during the course of a delirium. However, a dementia and a delirium may both be diagnosed if the dementia is present at times when the delirium is not present. Dementia may be etiologically related to a general medical condition, to the persisting effects of substance use (including toxin exposure), or to a combination of these factors.

Memory impairment is required to make the diagnosis of a dementia and is a prominent early symptom (Criterion Al). Individuals with dementia become impaired in their ability to learn new material, or they forget previously learned material. Most individuals with dementia have both forms of memory impairment, although it is sometimes difficult to demonstrate the loss of previously learned material early in the course of the disorder. They may lose valuables like wallets and keys, forget food cooking on the stove, and become lost in unfamiliar neighbourhoods. In advanced stages of dementia, memory impairment is so

severe that the person forgets his or her occupation, schooling, birthday, family members, and sometimes even name.

Memory may be formally tested by asking the person to register, retain, recall, and recognize information. The ability to learn new information may be assessed by asking the individual to learn a list of words. The individual is requested to repeat the words (registration), to recall the information after a delay of several minutes (retention, recall), and to recognize the words from a multiple list (recognition). Individuals with difficulty learning new information are not helped by clues or prompts (e.g., multiple-choice questions) because they did not learn the material initially. In contrast, individuals with primarily retrieval deficits can be helped by clues and prompts because their impairment is in the ability to access their memories. Remote memory may be tested by asking the individual to recall personal information or past material that the individual found of interest (e.g., politics, sports, entertainment). It is also useful to determine (from the individual and informants) the impact of the memory disturbances on the individual's functioning (e.g., ability to work, shop, cook, pay bills, return home without getting lost).

Deterioration of language function (aphasia) may be manifested by difficulty producing the names of individuals and objects (Criterion A2a). The speech of individuals with aphasia may become vague or empty, with long circumlocutory phrases and excessive use of terms of indefinite reference such as "thing" and "it." Comprehension of spoken and written language and repetition of language may also be compromised. In the advanced stages of dementia, individuals may be mute or have a deteriorated speech pattern characterized by echolalia (i.e., echoing what is heard) or palilalia (i.e., repeating sounds or words over and over). Language is tested by asking the individual to name objects in the room (e.g., tie, dress, desk, lamp) or body parts (e.g., nose, chin, shoulder), follow commands ("Point at the door and then at the table"), or repeat phrases ("no ifs, ands, or buts").

Individuals with dementia may exhibit apraxia (i.e., impaired ability to execute motor activities despite intact motor abilities, sensory function, and comprehension of the required task) (Criterion A2b). They will be impaired in their ability to pantomime the use of objects (e.g., combing hair) or to execute known motor acts (e.g., waving goodbye). Apraxia may contribute to deficits in cooking, dressing, and drawing. Motor skill disturbances may be tested by asking the individual to execute motor functions (e.g., to show how to brush teeth, to copy intersecting pentagons, to assemble blocks, or to arrange sticks in specific designs).

Individuals with dementia may exhibit agnosia (i.e., failure to recognize or identify objects despite intact sensory function) (Criterion A2c). For example, the individual may have normal visual acuity but lose the ability to recognize objects such as chairs or pencils. Eventually they may be unable to recognize family members or even their own reflection in the mirror. Similarly, they may have normal tactile sensation, but be unable to identify objects placed in their hands by touch alone (e.g., a coin or keys).

Disturbances in executive functioning are a common manifestation of dementia (Criterion A2d) and may be related specially to disorders of the frontal lobe or associated subcortical pathways. Executive functioning involves the ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behaviour. Impairment in abstract thinking may be manifested by the individual having difficulty coping with novel tasks and avoiding situations that require the processing of new and complex information.

The ability to abstract can be formally assessed by asking the person to find similarities or differences between related words. Executive dysfunction is also evident in a reduced ability to shift mental sets, to generate novel verbal or nonverbal information, and to execute serial motor activities. Tests for executive function include asking the individual to count to 10, recite the alphabet, subtract serial 7s, state as many animals as possible in 1 minute, or draw a continuous line consisting of alternating m's and n's. It is also useful to determine (from the individual and informants) the impact of the disturbances in executive functioning on the individual's daily life (e.g., ability to work, plan activities, budget).

The items in both Criterion Al (memory impairment) and Criterion A2 (aphasia, apraxia, agnosia, or disturbance in executive functioning) must be severe enough to cause significant impairment in social or occupational functioning (e.g., going to school, working, shopping, dressing, bathing, handling finances, and other activities of daily living) and must represent a decline from a previous level of functioning (Criterion B).

The nature and degree of impairment are variable and often depend on the particular social setting of the individual. The same level of cognitive impairment may significantly impair an individual's ability to perform a complex job, but not a job that is less demanding. Standardized published rating scales that measure physical maintenance (e.g., personal hygiene), intellectual functioning, and the ability to use implements or tools (e.g., telephone, washing machine) can be used to measure the severity of impairment.

Dementia is not diagnosed if these symptoms occur exclusively during the course of a delirium. However, a delirium may be superimposed on a pre-existing dementia, in which case both diagnoses should be given.

16.2.2 Associated Features and Disorders

16.2.2.1 Associated descriptive features and mental disorders

Individuals with dementia may become spatially disoriented and have difficulty with spatial tasks. Visuospatial functioning can be assessed by asking the individual to copy drawings, such as a circle, overlapping pentagons, and a cube. Poor judgment and poor insight are common in dementia. Individuals may exhibit little or no awareness of memory loss or other cognitive abnormalities. They may make unrealistic assessments of their abilities and make plans that are not congruent with their deficits and prognosis (e.g., planning to start a new business). They may underestimate the risks involved in activities (e.g., driving). Occasionally, they may harm others by becoming violent. Suicidal behaviour may occur, particularly in early stages when the individual is more capable of carrying out a plan of action. Dementia is sometimes accompanied by motor disturbances of gait leading to falls. Some individuals with dementia show disinhibited behaviour, including making inappropriate jokes, neglecting personal hygiene, exhibiting undue familiarity with strangers, or disregarding conventional rules of social conduct. Slurred speech may occur in dementia that is associated with subcortical pathology such as Parkinson's disease, Huntington's disease, and some cases of Vascular Dementia. The multiple cognitive impairments of dementia are often associated with anxiety, mood, and sleep disturbances. Delusions are common, especially those involving themes of persecution (e.g., that misplaced possessions have been stolen). Hallucinations can occur in all sensory modalities, but visual hallucinations are most common. Delirium is frequently superimposed on dementia because the underlying brain disease may increase susceptibility to confusional states that may be produced by medications or other concurrent general medical conditions. Individuals with dementia may be especially vulnerable to physical stressors (e.g., illness or minor surgery) and psychosocial stressors (e.g., going to the hospital, bereavement), which may exacerbate their intellectual deficits and other associated problems.

16.2.2.2 Associated laboratory findings

A discussion of associated laboratory findings that are specific to types of dementia is included in the text for each dementia. Invariably there are abnormalities in cognitive and memory functioning, which can be assessed using mental status examinations and neuropsychological testing. Neuroimaging may aid in the differential diagnosis of dementia. Computed tomography (CT) or magnetic resonance imaging (MRI) may reveal cerebral atrophy, focal brain lesions (cortical strokes, tumours, subdural hematomas), hydrocephalus, or periventricular ischemic brain injury. Functional imaging such as positron-emission tomography (PET) or single photon emission computed tomography (SPECT) are not routinely used in the evaluation of dementia, but may provide useful differential diagnostic information (e.g., parietal lobe changes in Alzheimer's disease or frontal lobe alterations in

frontal lobe degenerations) in individuals without evidence of structural changes on CT or MRI scans.

16.2.2.3 Associated physical examination findings and general medical conditions

The associated physical examination findings of dementia depend on the nature, location, and stage of progression of the underlying pathology. The most common cause of dementia is Alzheimer's disease, followed by vascular disease, and then by multiple aetiologies. Other causes of dementia include Pick's disease, normal-pressure hydrocephalus, Parkinson's disease, Huntington's disease, traumatic brain injury, brain tumours, anoxia, infectious disorders (e.g., human immunodeficiency virus [HIV], syphilis), prion diseases (e.g., Creutzfeldt-Jakob disease), endocrine conditions (e.g., hypothyroidism, hypercalcemia, hypoglycemia), vitamin deficiencies (e.g., deficiencies of thiamine, niacin, vitamin 612), immune disorders (e.g., polymyalgia rheumatica, systemic lupus erythematosus), hepatic conditions, metabolic conditions (e.g., Kufs' disease, adrenoleukodystrophy, metachromatic leukodystrophy, and other storage diseases of adulthood and childhood), and other neurological conditions (e.g., multiple sclerosis).

16.2.3 Specific Culture and Age Features

Cultural and educational background should be taken into consideration in the evaluation of an individual's mental capacity. Individuals from certain backgrounds may not be familiar with the information used in certain tests of general knowledge (e.g., names of presidents, geographical knowledge), memory (e.g., date of birth in cultures that do not routinely celebrate birthdays), and orientation (e.g., sense of place and location may be conceptualized differently in some cultures). The prevalence of different causes of dementia (e.g., infections, nutritional deficiencies, traumatic brain injury, endocrine conditions, cerebrovascular diseases, seizure disorders, brain tumours, substance abuse) varies substantially across cultural groups.

The age at onset of dementia depends on the aetiology, but is usually late in life, with highest prevalence above age 85 years. A significant deterioration in memory and in multiple cognitive skills, which is necessary for the diagnosis of dementia, may be difficult to document in very young children. Thus, the diagnosis of dementia may not be practical until the child is older (usually between ages 4 and 6 years). In individuals under age 18 years with Mental Retardation, an additional diagnosis of a dementia should be made only if the condition is not characterized satisfactorily by the diagnosis of Mental Retardation alone. Dementia is uncommon in children and adolescents, but can occur as a result of general medical conditions (e.g., head injury, brain tumours, HIV infection, strokes, adrenoleukodystrophies). Dementia in children may present as a deterioration in functioning

(as in adults) or as a significant delay or deviation in normal development. Deteriorating school performance may be an early sign.

16.2.4 Prevalence

Reported prevalence of dementia varies among epidemiological studies, depending on the ages of the subjects sampled; methods of determining the presence, severity, and type of cognitive impairment; and the regions or countries studied. Community studies estimated a 1-year prospective prevalence of almost 3.0% with severe cognitive impairment in the adult population. The study assessed individuals with a brief instrument that assessed current cognitive status (the Mini-Mental State Exam), which does not identify specific diagnoses. It is estimated that 2%-4% of the population over age 65 years have Dementia of the Alzheimer's Type, with other types being much less common. The prevalence of dementia, especially Dementia of the Alzheimer's Type and Vascular Dementia, increases with age, particularly after age 75 years, with a prevalence of 20% or more over age 85 years.

16.2.5 Course

Historically, the term dementia implied a progressive or irreversible course. The DSM-IV definition of dementia, however, is based on the pattern of cognitive deficits and carries no connotation concerning prognosis. Dementia may be progressive, static, or remitting. The reversibility of a dementia is a function of the underlying pathology and of the availability and timely application of effective treatment. The mode of onset and subsequent course of dementia also depend on the underlying aetiology. The level of disability depends not only on the severity of the individual's cognitive impairments but also on the available social supports. In advanced dementia, the individual may become totally oblivious to his or her surroundings and require constant care. Individuals with severe dementia are susceptible to accidents and infectious diseases, which often prove fatal.

16.2.6 Differential Diagnosis

Memory impairment occurs in both delirium and dementia. Delirium is also characterized by a reduced ability to maintain and shift attention appropriately. The clinical course can help to differentiate between delirium and dementia. Typically, symptoms in delirium fluctuate and symptoms in dementia are relatively stable. Multiple cognitive impairments that persist in an unchanged form for more than a few months suggest dementia rather than delirium. Delirium may be superimposed on a dementia, in which case both disorders are diagnosed. In situations in which it is unclear whether the cognitive deficits are due to a delirium or a

dementia, it may be useful to make a provisional diagnosis of delirium and observe the person carefully while continuing efforts to identify the nature of the disturbance.

An amnestic disorder is characterized by severe memory impairment without other significant impairments of cognitive functioning (i.e., aphasia, apraxia, agnosia, or disturbances in executive functioning).

The presumed aetiology determines the specific dementia diagnosis. If the clinician has determined that the dementia is due to multiple aetiologies, multiple codes based on the specific dementias and their aetiologies should be used (see Dementia Due to Multiple Aetiologies, p. 154). In Vascular Dementia, focal neurological signs (e.g., exaggeration of deep tendon reflexes, extensor plantar response) and laboratory evidence of vascular disease judged to be related to the dementia are present. The clinical course of Vascular Dementia is variable and typically progresses in stepwise fashion. The presence of Dementia Due to Other General Medical Conditions (e.g., Pick's disease, HIV) requires evidence from the history, physical examination, and appropriate laboratory tests that a general medical condition is etiologically related to the dementia. The onset of the deterioration (gradual or sudden) and its course (acute, subacute, or chronic) may be useful in suggesting the aetiology. For example, the severity of the impairment in cognitive functioning often remains static after head injury, encephalitis, or stroke.

Multiple cognitive deficits that occur only in the context of substance use are diagnosed as Substance Intoxication or Substance Withdrawal. If the dementia results from the persisting effects of a substance (i.e., a drug of abuse, a medication, or toxin exposure), then Substance-Induced Persisting Dementia is diagnosed. Other causes of dementia (e.g., Dementia Due to a General Medical Condition) should always be considered, even in a person with Substance Dependence. For example, head injury is not infrequent during substance use and may underlie the dementia. Dementia of the Alzheimer's Type is currently a diagnosis of exclusion, and other causes for the cognitive deficits (see above) must first be ruled out. In addition, the course is characterized by gradual onset and continuing cognitive decline. In those cases in which there is insufficient evidence to determine whether the dementia is due to a general medical condition or is substance induced, Dementia Not Otherwise Specified should be coded. Individuals may present with some but not all of the symptoms of dementia. Such presentations should be coded as Cognitive Disorder Not Otherwise Specified.

Mental Retardation is characterized by significantly subaverage current general intellectual functioning, with concurrent impairments in adaptive functioning and with an onset before age 18 years. Mental Retardation is not necessarily associated with memory impairment. In contrast, the age at onset of dementia is usually late in life. If the onset of the dementia is before age 18 years, both dementia and Mental Retardation may be diagnosed if the criteria for both disorders are met. Documenting a significant deterioration in memory and in other

cognitive skills, which is necessary for the diagnosis of dementia, may be difficult in persons under age 4 years. In individuals under age 18 years, the diagnosis of dementia should be made only if the condition is not characterized satisfactorily by the diagnosis of Mental Retardation alone.

Schizophrenia can also be associated with multiple cognitive impairments and a decline in functioning, but Schizophrenia is unlike dementia in its generally earlier age at onset, its characteristic symptom pattern, and the absence of a specific etiological general medical condition or substance. Typically, the cognitive impairment associated with Schizophrenia is less severe than that seen in Dementia.

Major Depressive Disorder may be associated with complaints of memory impairment, difficulty thinking and concentrating, and an overall reduction in intellectual abilities. Individuals sometimes perform poorly on mental status examinations and neuropsychological testing. Particularly in elderly persons, it is often difficult to determine whether cognitive symptoms are better accounted for by a dementia or by a Major Depressive Episode. This differential diagnosis may be informed by a thorough medical evaluation and an evaluation of the onset of the disturbance, the temporal sequencing of depressive and cognitive symptoms, the course of illness, family history, and treatment response. The premorbid state of the individual may help to differentiate "pseudodementia" (i.e., cognitive impairments due to the Major Depressive Episode) from dementia. In dementia, there is usually a premorbid history of declining cognitive function, whereas the individual with a Major Depressive Episode is much more likely to have a relatively normal premorbid state and abrupt cognitive decline associated with the depression. If the clinician determines that both a dementia and Major Depressive Disorder are present with independent aetiologies, both should be diagnosed.

Dementia must be distinguished from Malingering and Factitious Disorder. The patterns of cognitive deficits presented in Malingering and Factitious Disorder are usually not consistent over time and are not characteristic of those typically seen in dementia. For example, individuals with Factitious Disorder or Malingering manifesting as dementia may perform calculations while keeping score during a card game, but then claim to be unable to perform similar calculations during a mental status examination.

Dementia must be distinguished from the normal decline in cognitive functioning that occurs with aging (as in Age-Related Cognitive Decline). The diagnosis of dementia is warranted only if there is demonstrable evidence of greater memory and other cognitive impairment than would be expected due to normal aging processes and the symptoms cause impairment in social or occupational functioning.